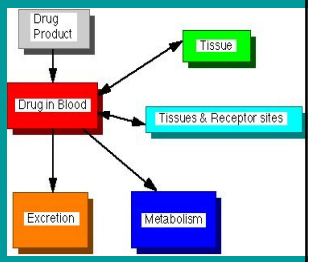
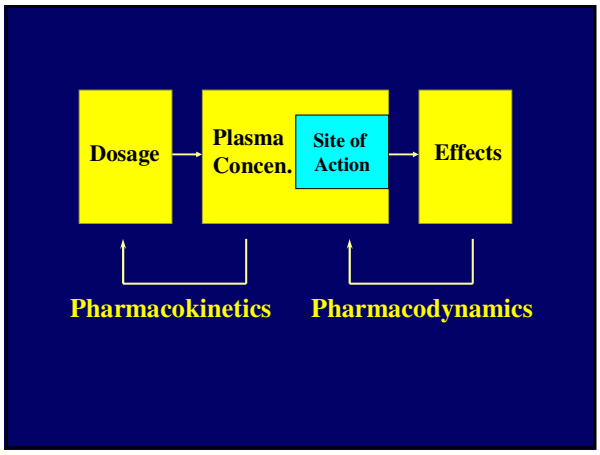
Pharmacokinetics

is the study of drug and/or metabolite **kinetics** in the body. It deals with a mathematical description of the rates of drug movement into, within and exit from the body. The body is a complex system and a drug undergoes many steps being **absorbed**, **distributed** through the body, **metabolized** or **excreted**. The drug also interacts with receptors and causes therapeutic and/or toxic responses.

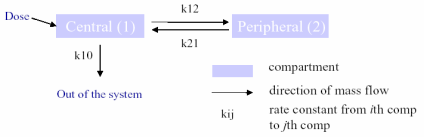


Concentration of drug in blood or at the receptor is variable of interest.



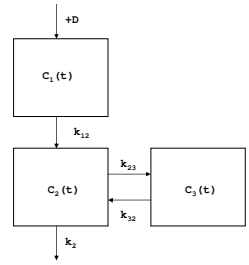
Compartmental Approach

- Data driven, physiological/anatomical correlates difficult
- Assume each comp. is well-mixed and kinetically homogeneous
- Based on the principle of mass balance
- First-order kinetics



Three-compartment model

$$\frac{dC_1}{dt} = -k_{12}C_1 + \sum_{i=1}^{n} D\delta(t - t_i)$$
$$\frac{dC_2}{dt} = k_{12}C_1 - (k_2 + k_{23}) \cdot C_2 + k_{32}C_3$$
$$\frac{dC_3}{dt} = k_{23}C_2 - k_{32}C_3$$



Stochastic three-compartment model

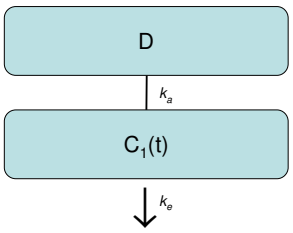
White (or other) noise can be added to any of the concentrations

$$\frac{dC_1}{dt} = -k_{12}C_1 + \sum_{i=1}^{n} D\delta(t - t_i) + \sigma_1\xi_1$$
$$\frac{dC_2}{dt} = k_{12}C_1 - (k_2 + k_{23}) \cdot C_2 + k_{32}C_3 + \sigma_2\xi_2$$
$$\frac{dC_3}{dt} = k_{23}C_2 - k_{32}C_3 + \sigma_3\xi_3$$

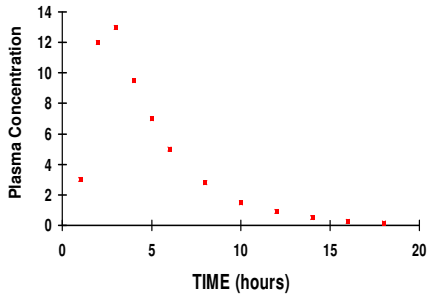
In drug compliance studies – variable is t_i

Single-compartment model with absorption

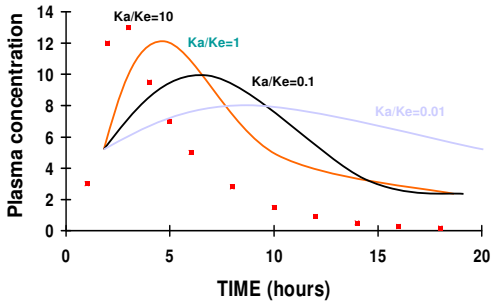
$$\frac{dD}{dt} = -k_a D, D(0) = D_0$$
$$D(t) = D_0 \exp(-k_a t)$$
$$\frac{dC_1}{dt} = k_a D - k_e C_1$$



Plasma concentration vs. time profile of a single dose of a drug ingested orally



Influence of Variations in Relative Rates of Absorption and Elimination on Plasma Concentration of an Orally Administered Drug



Multiple dosing

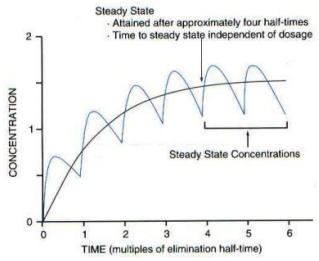
- On continuous steady administration of a drug, plasma concentration will rise fast at first then more slowly and reach a plateau, where:

  rate of administration = rate of elimination i.e. steady state is reached.

Changes are due to timing or dosing, then the steady state is disturbed and consequently the effect of therapy is modified. This is called Non-compliance or non-adherence

Steady state

As successive doses are administered, drug begins to accumulate in the body. With first order elimination, at a certain point in therapy, the amount of drug administered during a dosing interval exactly replaces the amount of drug excreted (rate in = rate out). When this equilibrium occurs, the peak and trough drug concentrations are the same for each additional dose given, steady-state is reached. The time required to reach steady-state is approximately **4 to 5 half-lives**.



"In HIV therapy, the biggest obstacle to successful treatment is adherence to medications. The method by which antiretroviral medications suppress the HIV virus necessitates a very strict regimen of medication. Drugs must be taken exactly as prescribed without missing doses. With any type of medication regimen, whether it is to treat HIV, diabetes, or high blood pressure, there are several reasons why people have difficulty adhering to their prescribed medications. Several studies have been done to identify these reasons:"

40% of people said they simply forgot
37% slept through a dose
34% were away from home
27% had made a change in their therapy routine
22% were too busy to take their meds
13% were too sick
10% were experiencing side effects
9% were suffering from depression

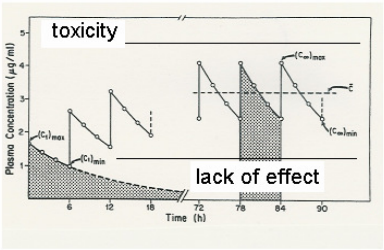
Motivation and Basic Terms

- Patient compliance with medication, both in timing and in dosing, is an important issue in evaluation the success of therapy.
- Noncompliance: - intentional (long term) and non-intentional (short term).
- The basic one-compartment model is investigated analytically under the steady-state conditions. It is assumed that the errors in the drug administration are mutually independent and that a new error in drug administration occurs always at the steady state. We concentrate on the effect of short-term noncompliance. ANTIBIOTICS
- Complex model is investigated by computer simulation
- The most frequent type of noncompliance is beside occasional omission (delay) of a dose a failure to take several consecutive doses.

Therapeutic Window

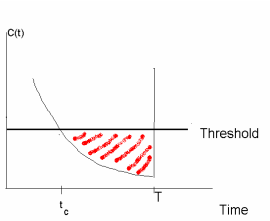
concentration in plasma yields optimal benefit at a minimal risk of toxicity

AUC – area under the curve, reflects therapeutic effect

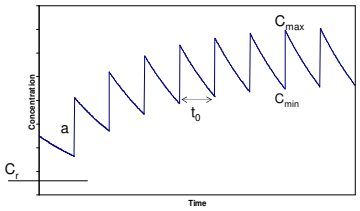


Area under the threshold

not only the time spent outside the therapeutic window but the depth of the curve is important



Basic Model - Fast absorption rate



Basic Model - Fast absorption rate

The concentration after administration at time zero is

$$c(t) = (a + c_r)exp(-kt)\ ,$$

The asymptotic maximum and minimum

$$C_1 = \frac{a}{1 - exp(-kt_0)}$$

and

$$C_0 = \frac{aexp(-kt_0)}{1 - exp(-kt_0)}$$

t_0 is the interval in regular dosing.

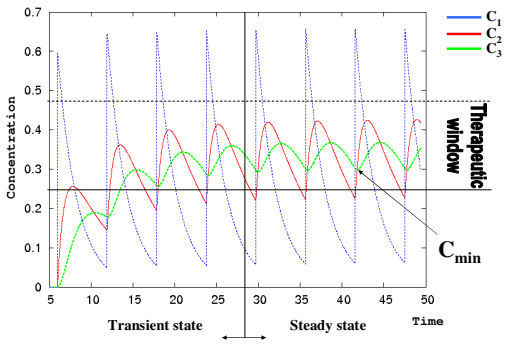
Drug concentration influenced by noncompliance Distribution of max and min

t_0 is replaced by a random variable T

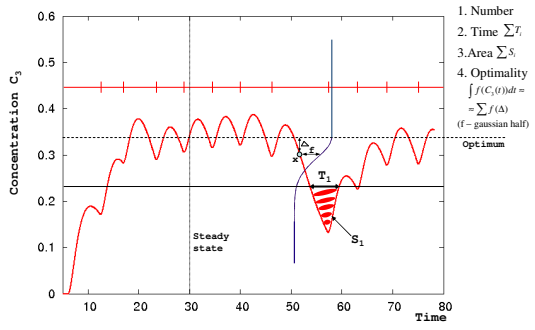
$$Prob(C_{\max} < c) = Prob(T > -\frac{ln(1 - \frac{a}{c})}{k})$$

$$Prob(C_{\min} < c) = Prob(T > \frac{ln(1 + \frac{a}{c})}{k}),$$

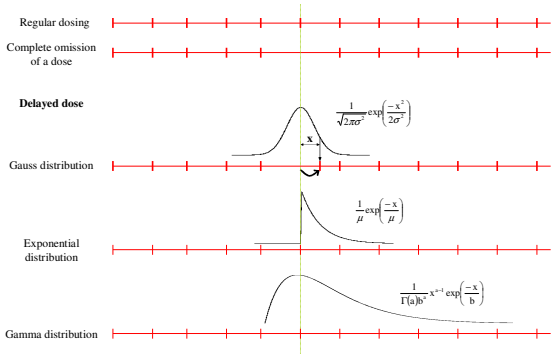
Regular drug application



Noncompliance measures



Types of dose omission



Types of Fluctuation

(a) symmetrical, $E(T) = t_0$, $\sigma \ll 3t_0$

$$g(t) = \frac{exp(-\frac{(t-t_0)^2}{2\sigma^2})}{\sqrt{2\pi\sigma^2}},$$

(b) asymmetrical, T defined on $(t_0 - \epsilon, 2t_0)$, $E(T) = t_0$.
Gamma distribution with parameter $\kappa \geq 1$, truncated at $2t_0$ and normalized

$$g(t) = \frac{\lambda(\lambda(t + t_0 - \epsilon))^{\kappa-1} exp(-\lambda(t + t_0 - \epsilon))}{(\kappa - 1)!q},$$

where $q = \int_{t_0-\epsilon}^{2t_0} g(t)dt$.
(c) delay longer than t_0. The shifted exponential distribution

$$g(t) = \lambda exp(-\lambda(t - t_0)), t > t_0$$

After the scheduled time of the dose at time t_0, it is taken at random time with constant hazard rate.

MODELING THE INFLUENCE OF NON-ADHERENCE ON ANTIBIOTIC EFFICACY: APPLICATION TO CIPROFLOXACIN

- Multiple dosing, 250 mg every 12 hours or 500 mg every 24 hours, of orally applied ciprofloxacin over ten days.
- Mortality rate of sensitive bacterial population (sigmoidal)

$$\mu(t) = \frac{(\Psi_{\max}{}^S - \Psi_{\min}{}^S)\frac{C(t)}{zMIC}}{\frac{C(t)}{zMIC} - \frac{\Psi_{\min}{}^S}{\Psi_{\max}{}^S}}$$

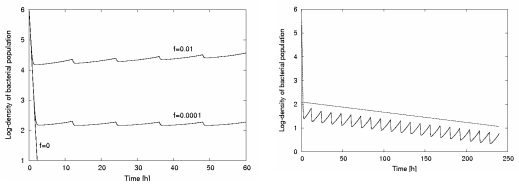
Bacterial population under treatment

- a new bacterial cell arises, the probability, *f*, that it will be resistant

$$\frac{dX^S(t)}{dt} = (1-f)\left(\Psi_{\max}{}^S X^S(t) + \Psi_{\max}{}^T X^T(t)\right) - \mu(t)X^S(t)$$

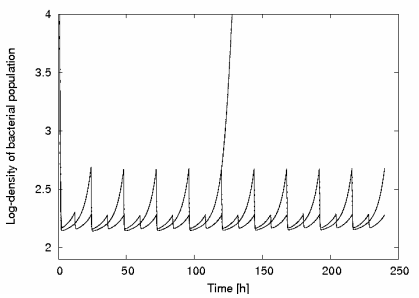
$$\frac{dX^T(t)}{dt} = f\left(\Psi_{\max}{}^S X^S(t) + \Psi_{\max}{}^T X^T(t)\right)$$

Decrease (left) in bacterial density during ciprofloxacin therapy 250mg/12h for regular dosing. Effect of innate capability to contribute to bacterial kill (*f*=0.0001, innate killing rate *mT*=0.01 [1/h]) . The line gives the density of resistant population, the saw-like curve is the density of sensitive bacterial population



Bacterial density during ciprofloxacin therapy for 500 mg/24 h regular dosing (higher maxima), regular dosing 250mg/12h (lower maxima).

Discontinuation of the treatment at time 100 is illustrated



Drug – receptor interaction

- Most drugs combine with specific sites on macromolecules (e.g. cell membrane components) by precise physiochemical interactions between specific chemical groups of the drug. These sites are termed **receptors.**
- **Pharmacodynamics**

Theory and assumptions of drug-receptor interaction

- Combination or binding to receptor causes some event which leads to the response.
- Response to a drug is graded or dose-dependent. Drug receptor interaction follows simple mass-action relationships, i.e., only one drug molecule occupies each receptor site and binding is reversible.
- For a given drug, the magnitude of response is directly proportional to the fraction of total receptor sites occupied by drug molecules (i.e. the occupancy assumption).
- The number of drug molecules is assumed to be much greater than the number of receptor sites.

Drug-receptor

- Combination of drug with a receptor produces a specific response. "lock and key".
- Drug-receptor interactions are analogous to enzyme-substrate interactions. Most of the same principles apply.
- Drug-receptor interactions with characteristics outlined above can be treated with an equation analogous to the Michaelis Menten equation utilized for enzyme-substrate interactions

$$D + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DR \xrightarrow{k_3} \text{Effect}$$

The Log Dose-Response Curve

- Advantages of expression as log versus response
  - Dose-response relationship expressed as a nearly straight line over a large range of drug doses.
  - Wide range of doses can be plotted on a single graph, allowing easy comparison of different drugs.
  - Use of log dose-response curves to compare different drugs which produce the same response

Typical log dose-response curve