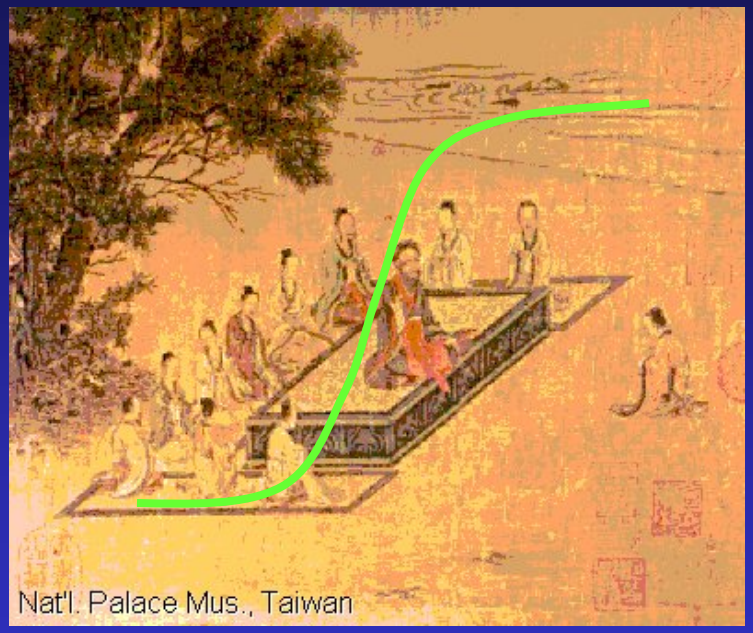
Asian PK/PD Educational Workshop



The general concept of pharmacodynamics

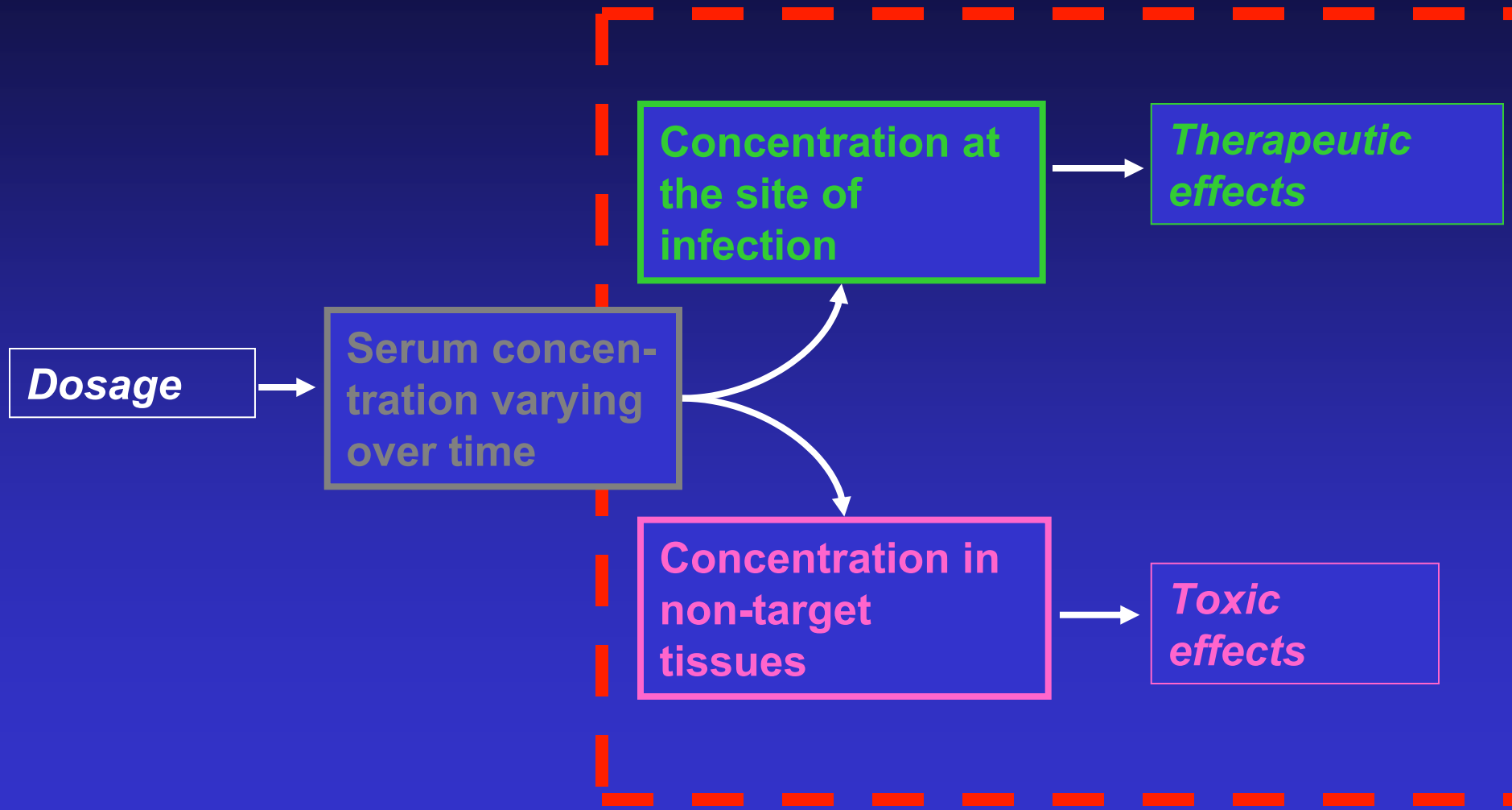
- modeling the antibacterial effects
- relations PK / PD

This part uses material from presentations of H. Derendorf (Gainesville, Fla.) made at the 2001 and 2001 ISAP Educational Workshops

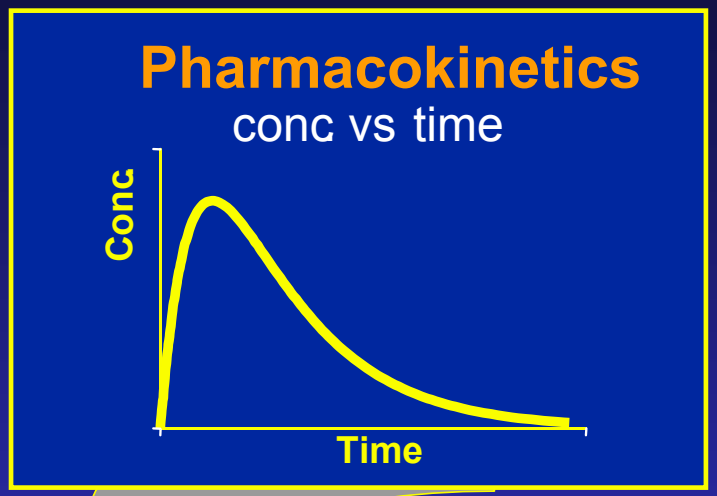
What is pharmacodynamics ?

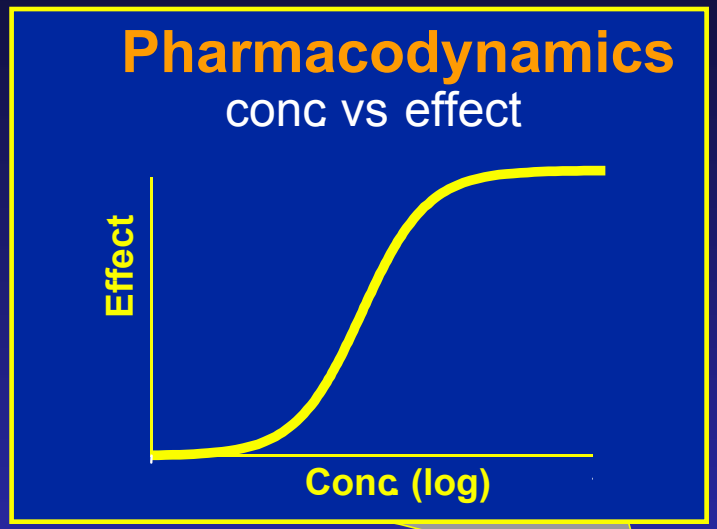
What the drug does to the body ...

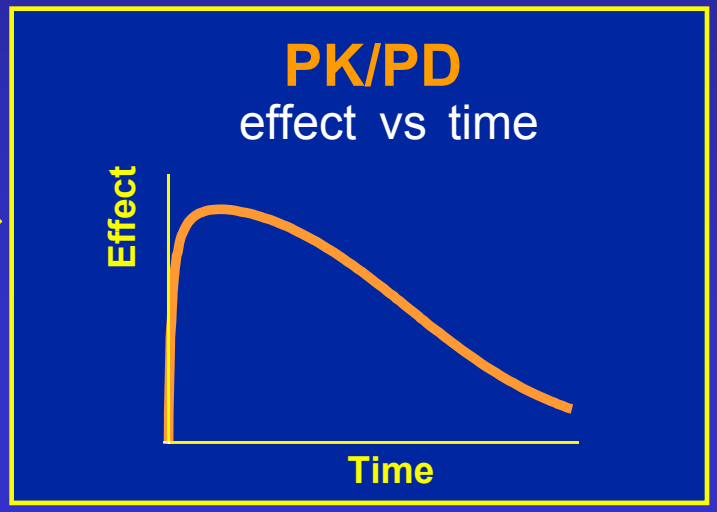
Pharmacokinetics Pharmacodynamics



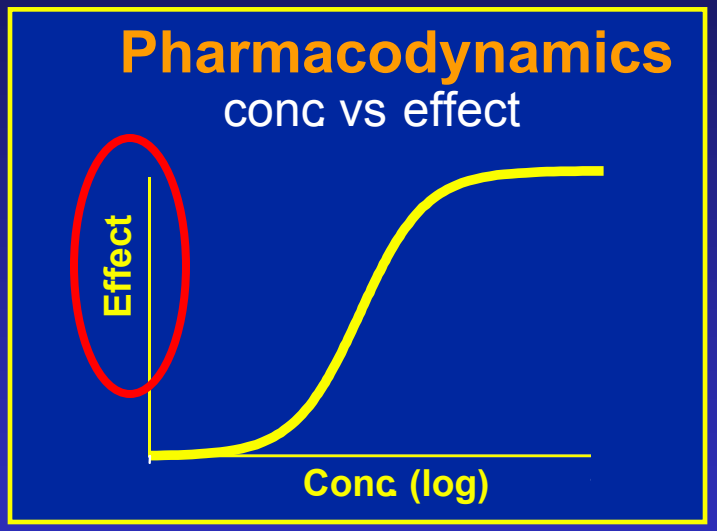
Pharmacokinetics - Pharmacodynamics







Pharmacoynamics : what is the end-point ?



1. therapeutical result
   - clinical ...
   - laboratory ...

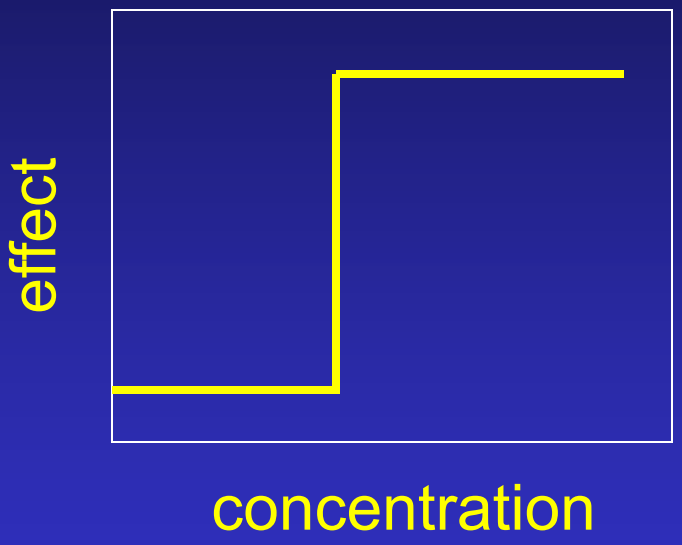
2. Biomarker

   Drug- or disease-induced measurable physiological, pathophysiological or biochemical change

3. Surrogate end-point

   Biomarker that has predictive value for therapeutic outcome

Pharmacodynamics : which are the models ?

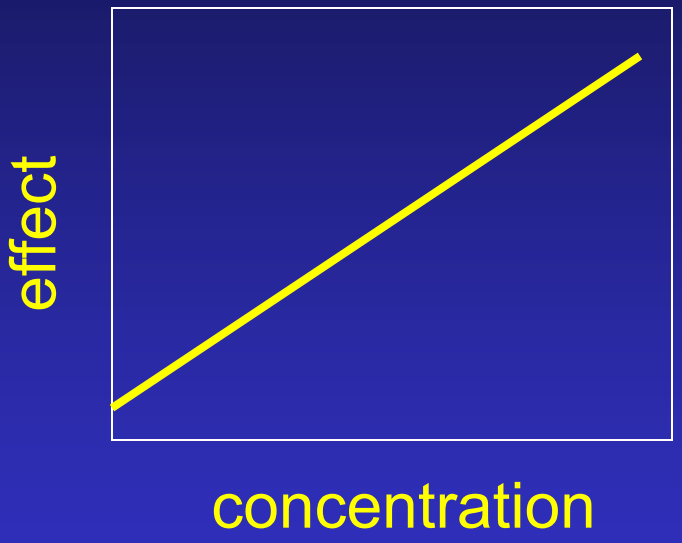


The **yes / no** model

- sharp threshold
- maximal effect immediately observed

This is the model assumed by
- **the sensitivity breakpoints approach !!**
- **the cured / non-cured clinical endpoint !!**

Pharmacodynamics : which are the models ?

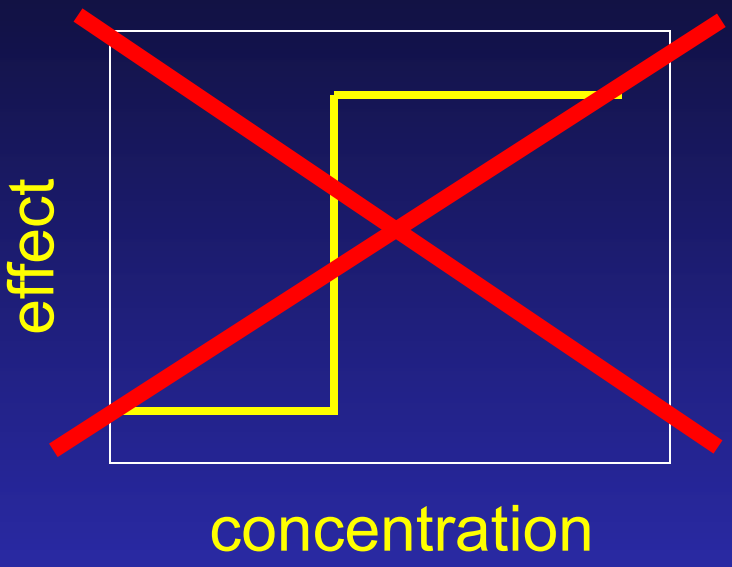


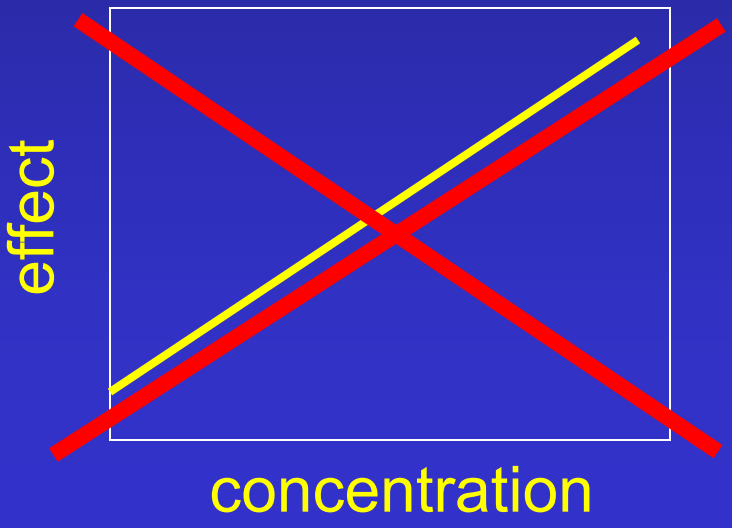
The **linear** model

- continuouly increasing effect
- effect matches dosing

This is the model assumed by the "higher dosing in severe infections" approach

Pharmacodynamics : which are the models ?



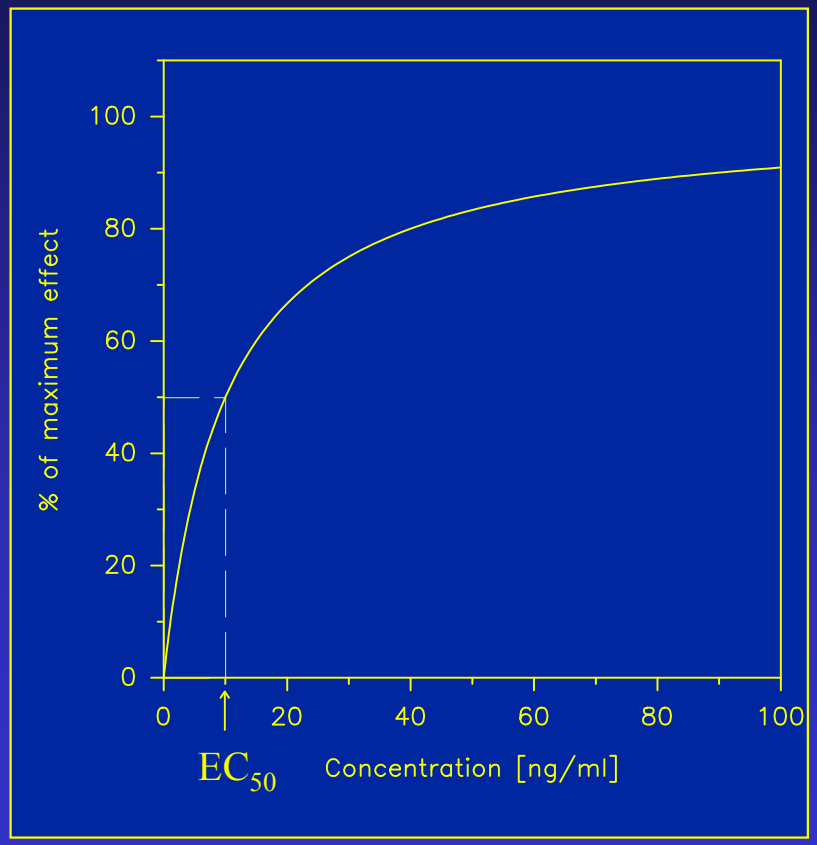


The **yes / no** and the **linear** models are almost never observed in true phamacological responses !!

Drugs (includig antibiotics) act indeed by **binding** to their targets,

and this binding is **saturable** ...

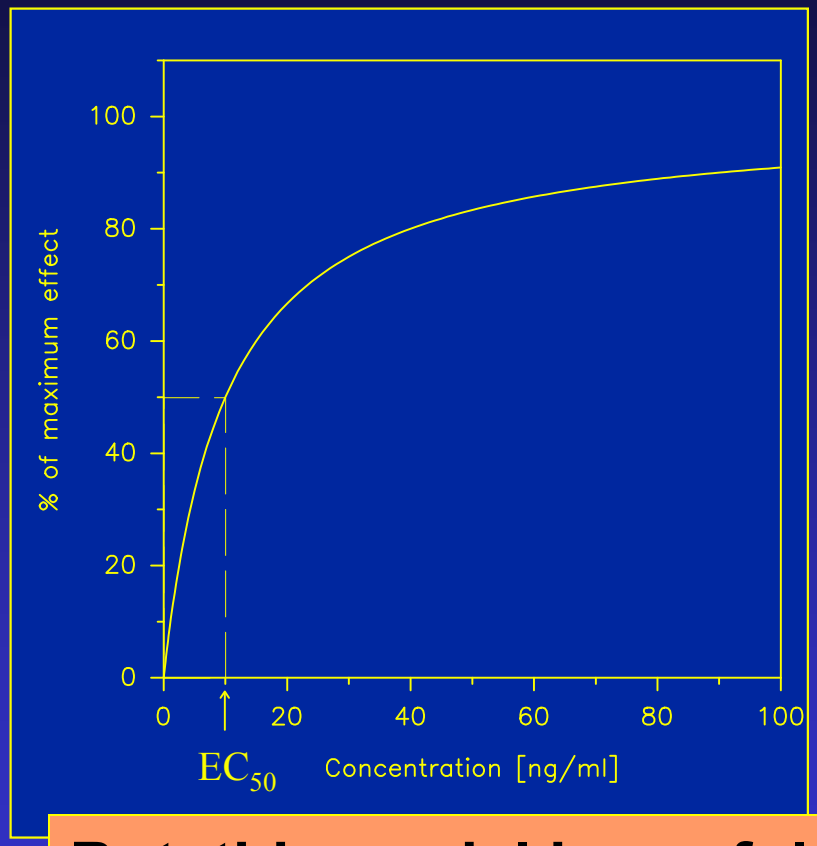
The E-max model ...



- Drug concentration increases at low initial values seem more effective than at large initial values
- There is a maximal effect corresponding to maximal receptor / target site occupancy

This is the classical model used for non-antiinfective drugs...

The conventional E-max model is inadequate…

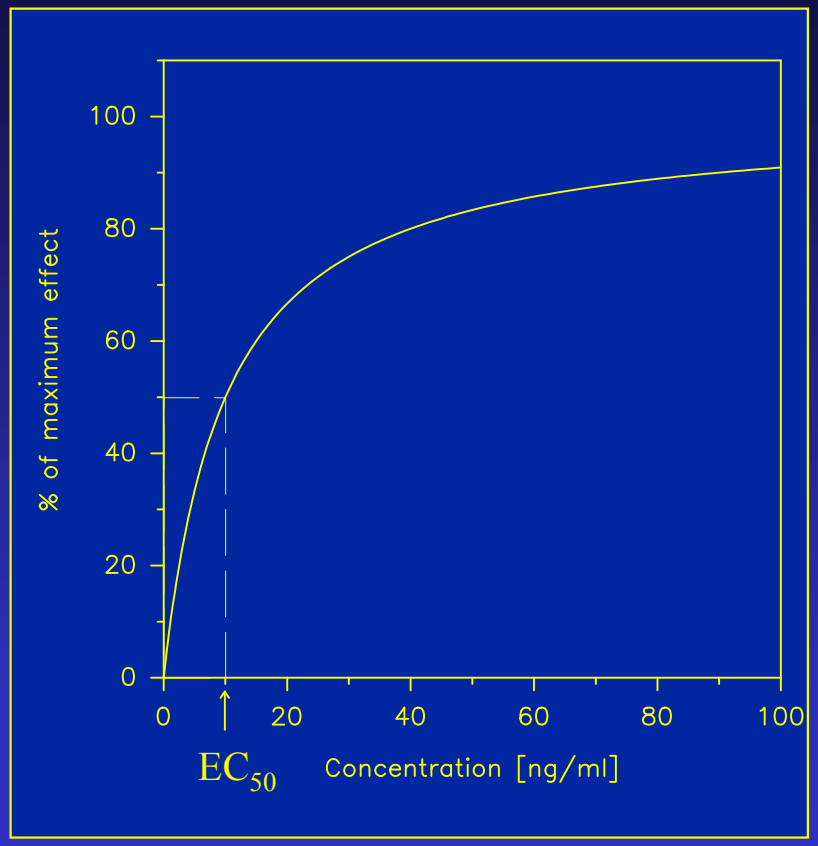


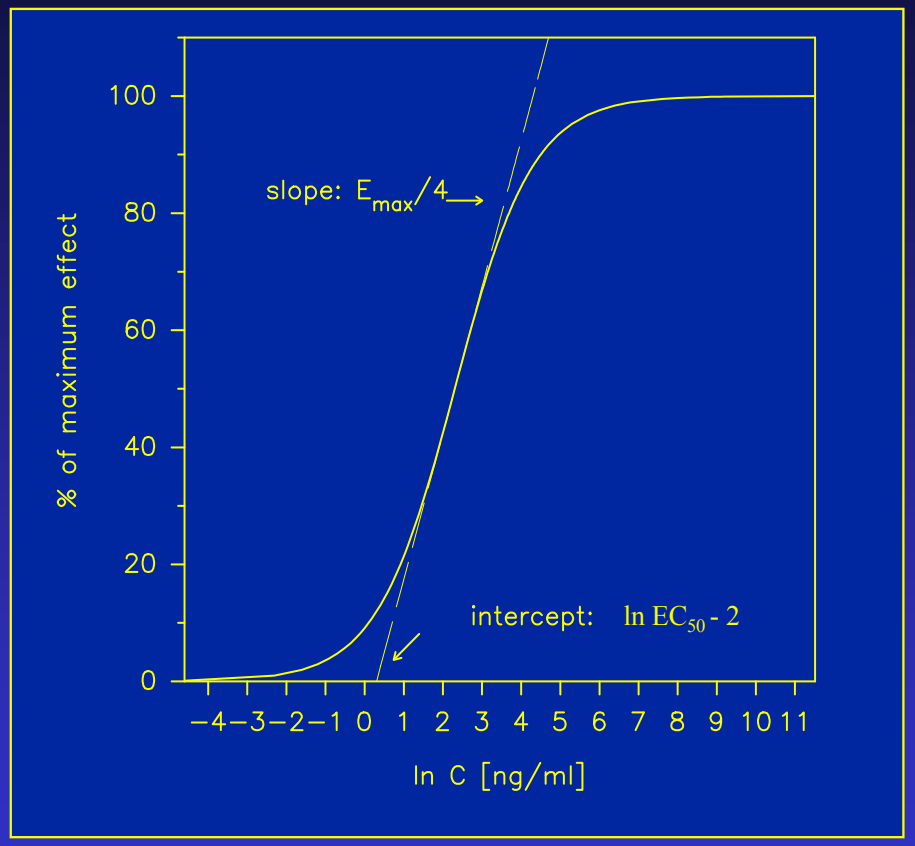
It ignores

- the **threshold** in effect seen when passing across the **MIC**
- the fact that antibiotics may be
  - **bacteriostatic**, or
  - **bactericidal**
- the influence of **time** ...

But, this model is useful to obtain a first description of dose-response effects … if appropriate corrections are introduced

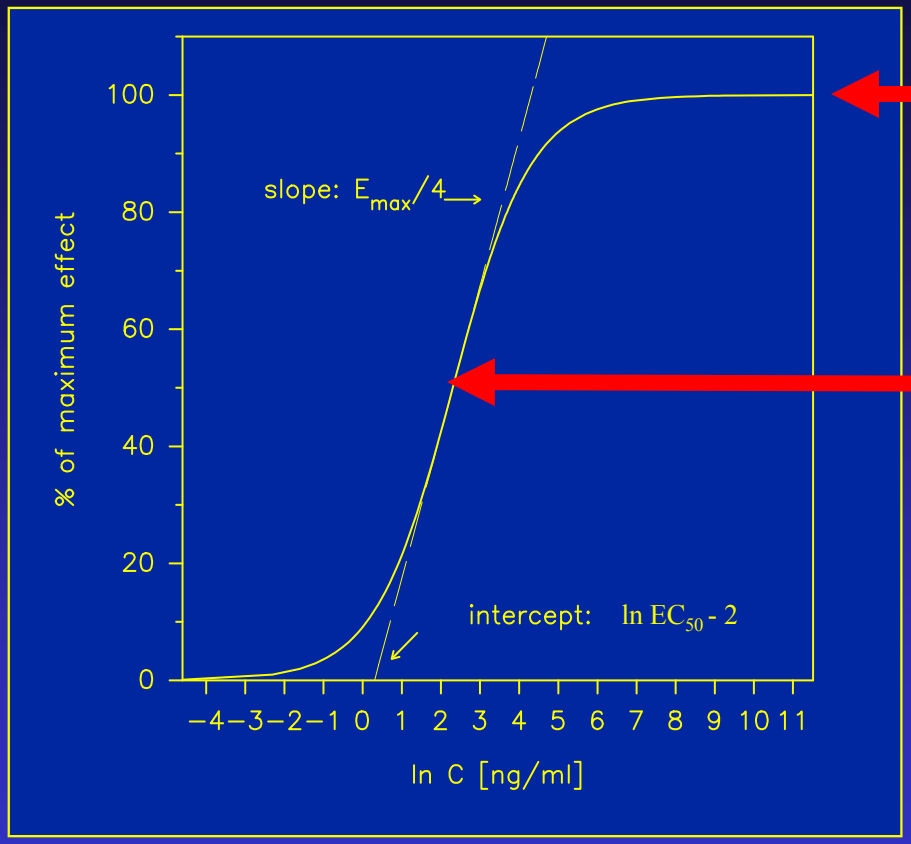
Mathematical representations of the E-max model





Arithmetic abcissa ⇒ Logarithmic abcissa

Why a logarithmic abcissa ...



E_{max}

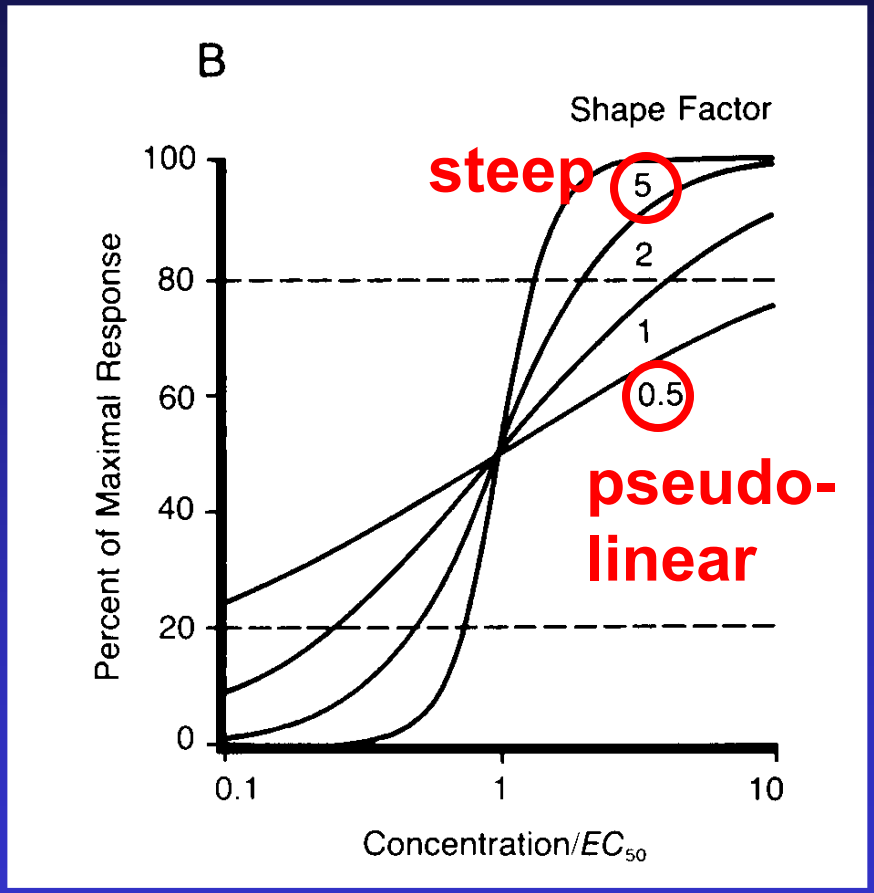
Maximal intensity of the response

$E_{50\%}$

$$E = \frac{E_{max} \cdot C^{n}}{EC_{50}^{n} + C^{n}}$$

Logarithmic abcissa

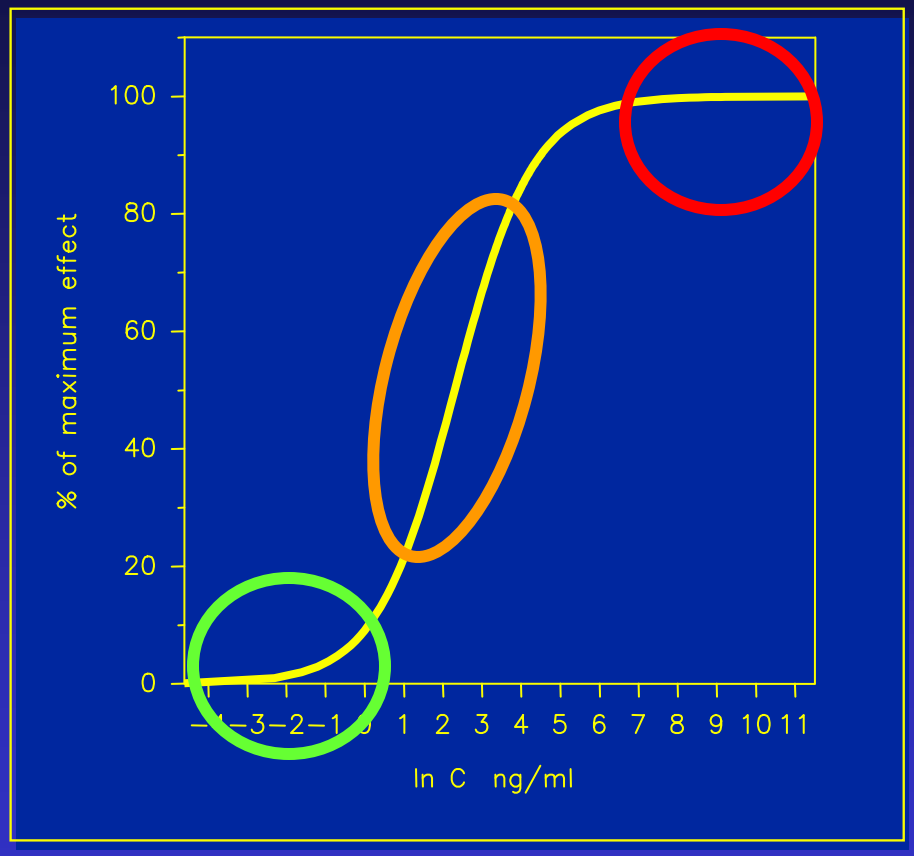
The E-max model may be used to incorporate the yes/no and the linear models within limits...



The "shape factor" describes the steepness of the response ...

$$E = \frac{E_{max} \cdot C^{n}}{EC_{50}^{n} + C^{n}}$$

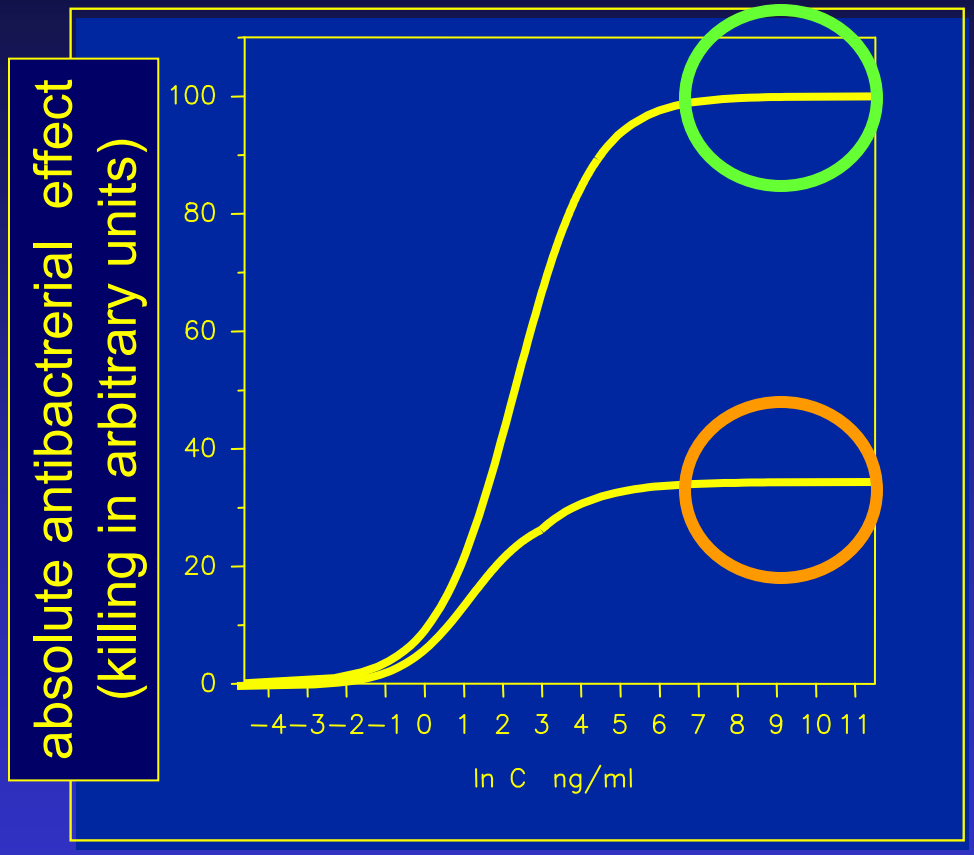
First points to consider in pharmacodynamic modeling of antibiotic response



- Emax
- steepness
- point of initial response

This is a description at a FIXED time only ...

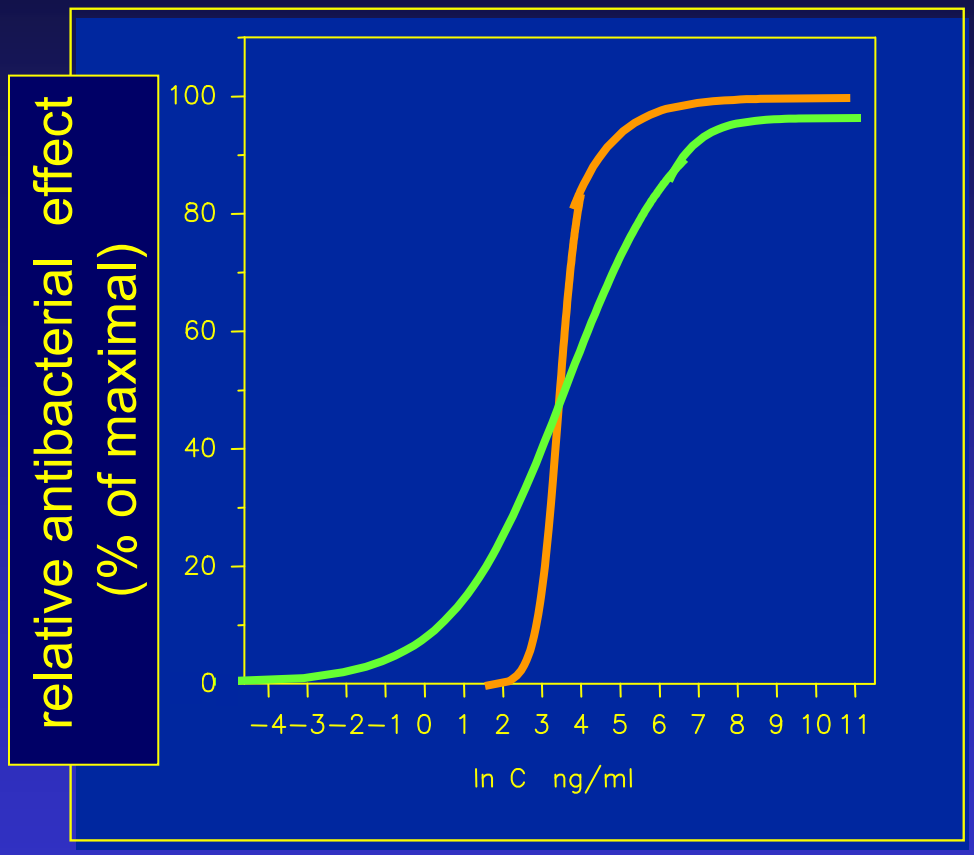
What means E-max (at a given time point) ?



Highly bactericidal
- fluoroquinolones
- aminoglycosides

Poorly bactericidal
- vancomycin
- macrolides
- tetracyclines

What does steepnes mean?

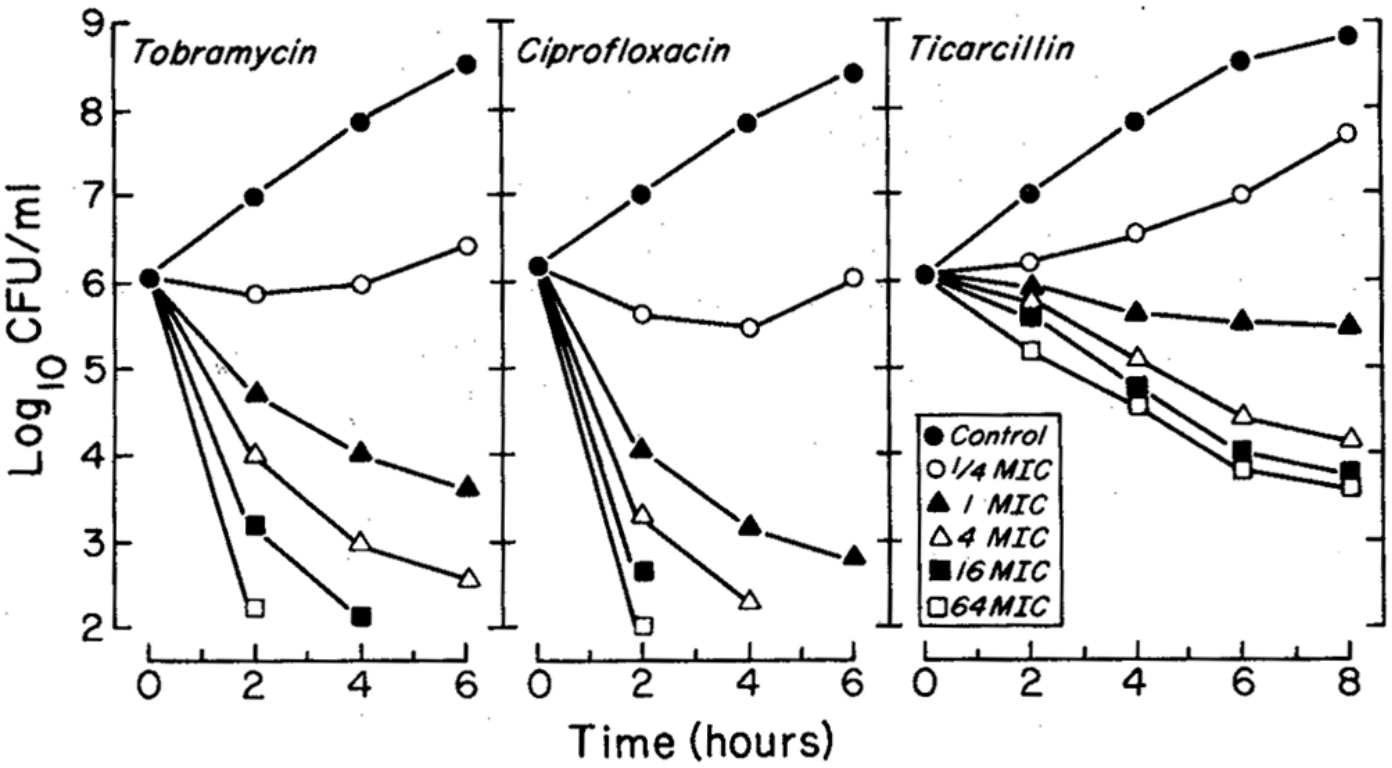


Highly concentration-dependent AB (as from MIC)
- fluoroquinolones
- aminoglycosides
- oritavancin

Poorly concentration-dependent AB
once above threshold (=MIC)
- β-lactams
- vancomycin

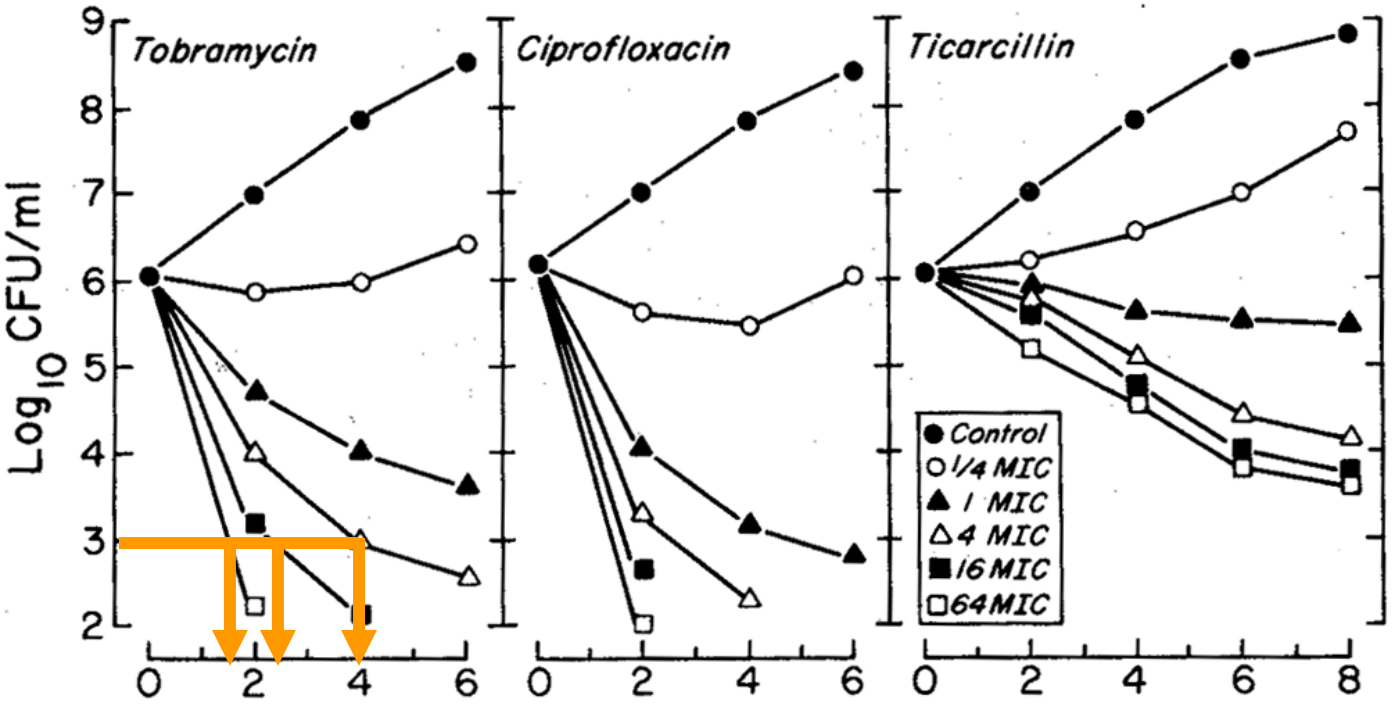
Pharmacodynamics : influence of time ...

All antibiotics are dependent on time...



Pharmacodynamics : influence of time ...

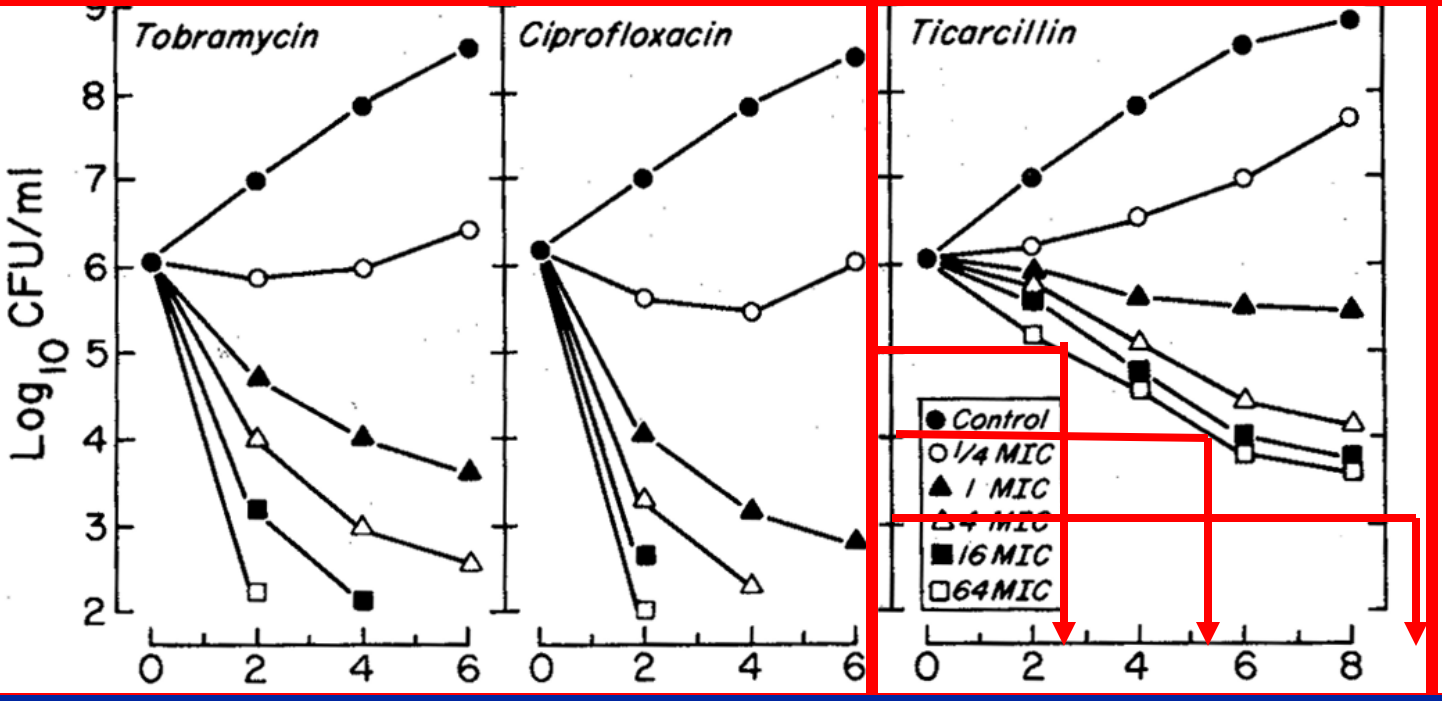
But time is relatively unimportant for highly concentration-dependent drugs



A 3 log reduction will be achieved in 4h, 2h or less depending on concentration...

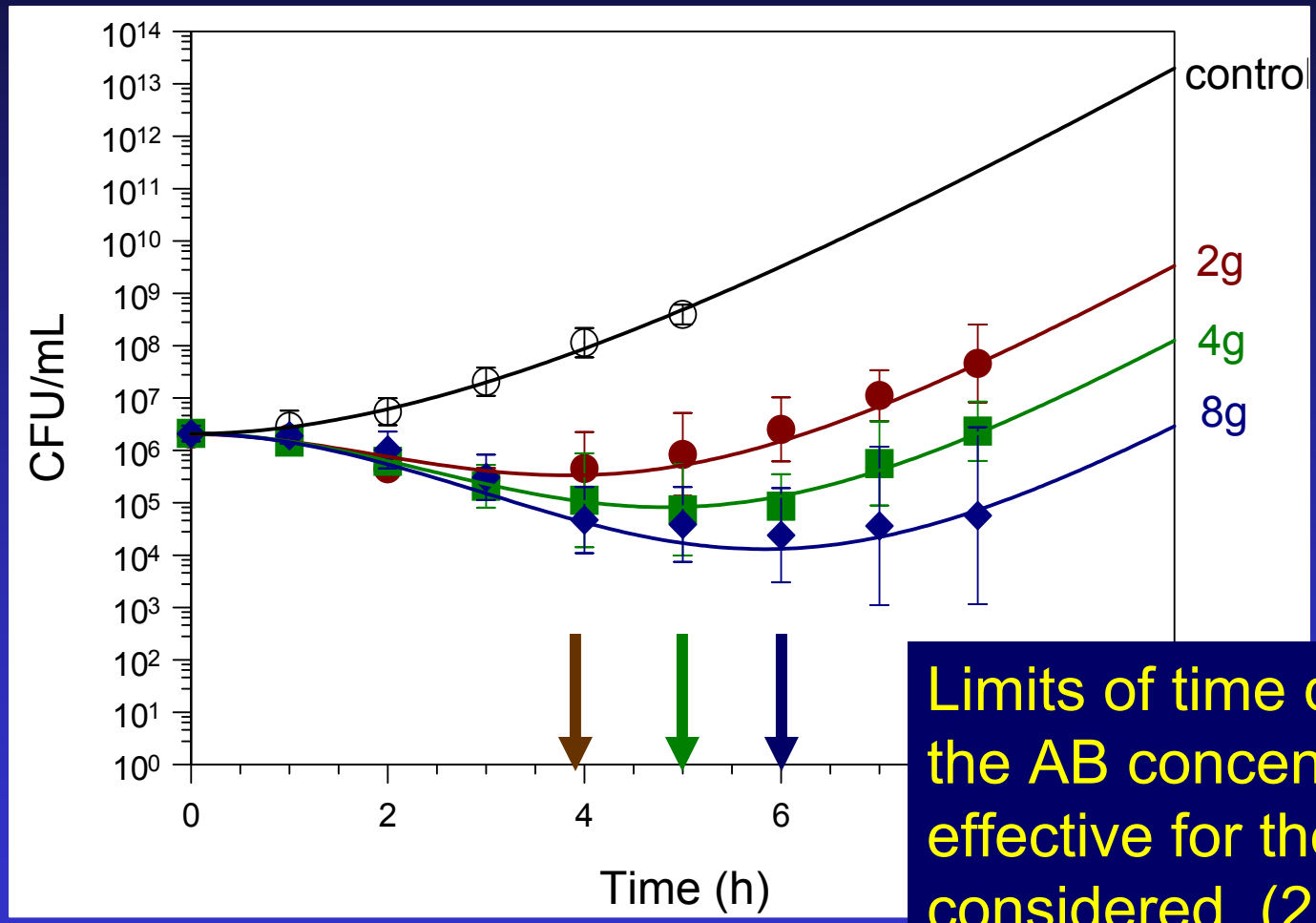
Pharmacodynamics : influence of time ...

Whereas time becomes the CRITICAL parameter for antibiotics with low concentration dependency



You always need more than 8h to achive a 3 logs kill

Time-dependent antibiotics with shott half-lifes are ineffective if not administered frequently

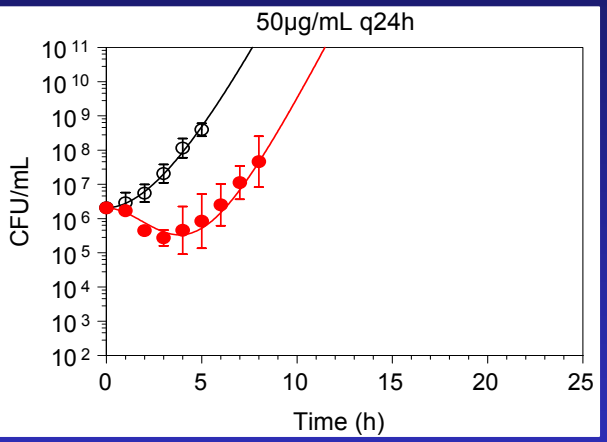


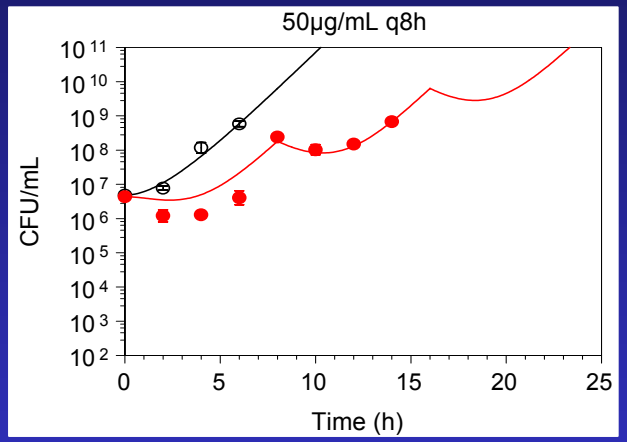
Piperacillin modeling as one single injection

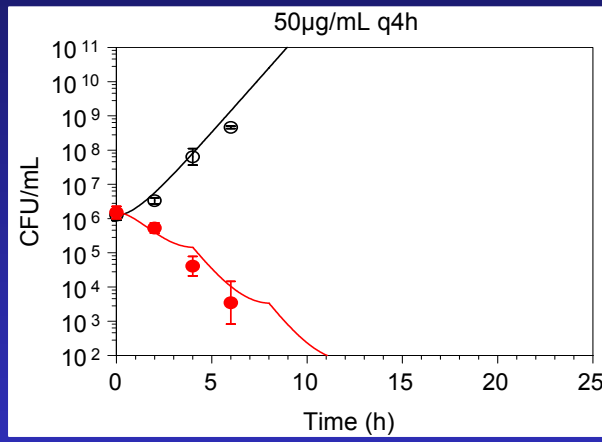
Limits of time during which the AB concentr. remains effective for the dose considered (2 g, 4 g, 8 g) ...

Low doses of poorly-concentration dependent antibiotics require frequent administration

Piperacillin modeled for a Cmax of 50 mg/L







once-a-day

q 8h

q 4h

This where we are now ...