Pharmacodynamics: the methods

- In vitro models
- Animal models
- Clinical studies
- Population studies

With the support of *Wallonie-Bruxelles-International*

Pharmacodynamics: the methods

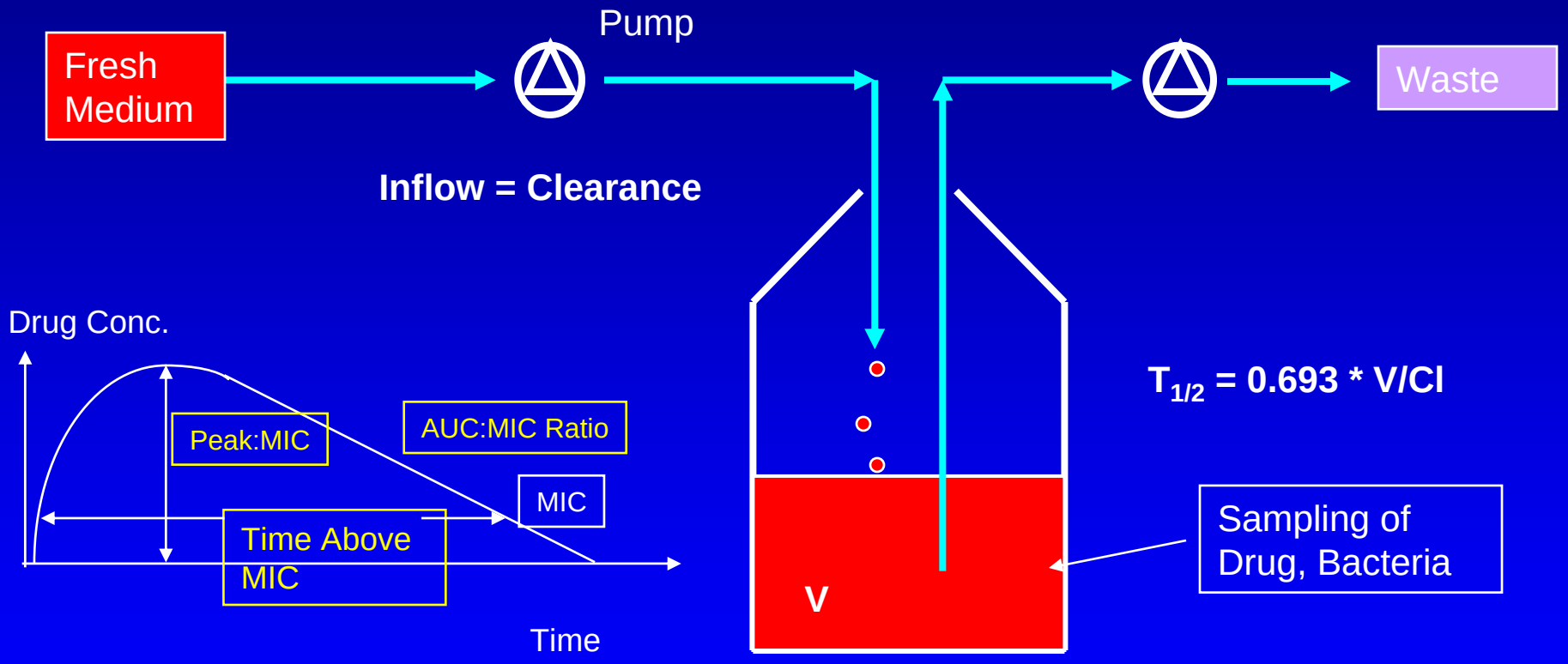
"un peu de tout …"

In vitro dynamic models

- Dilution models
- Diffusion models
- Hybrid models
- ‘Physiologic models’
- Intracellular models

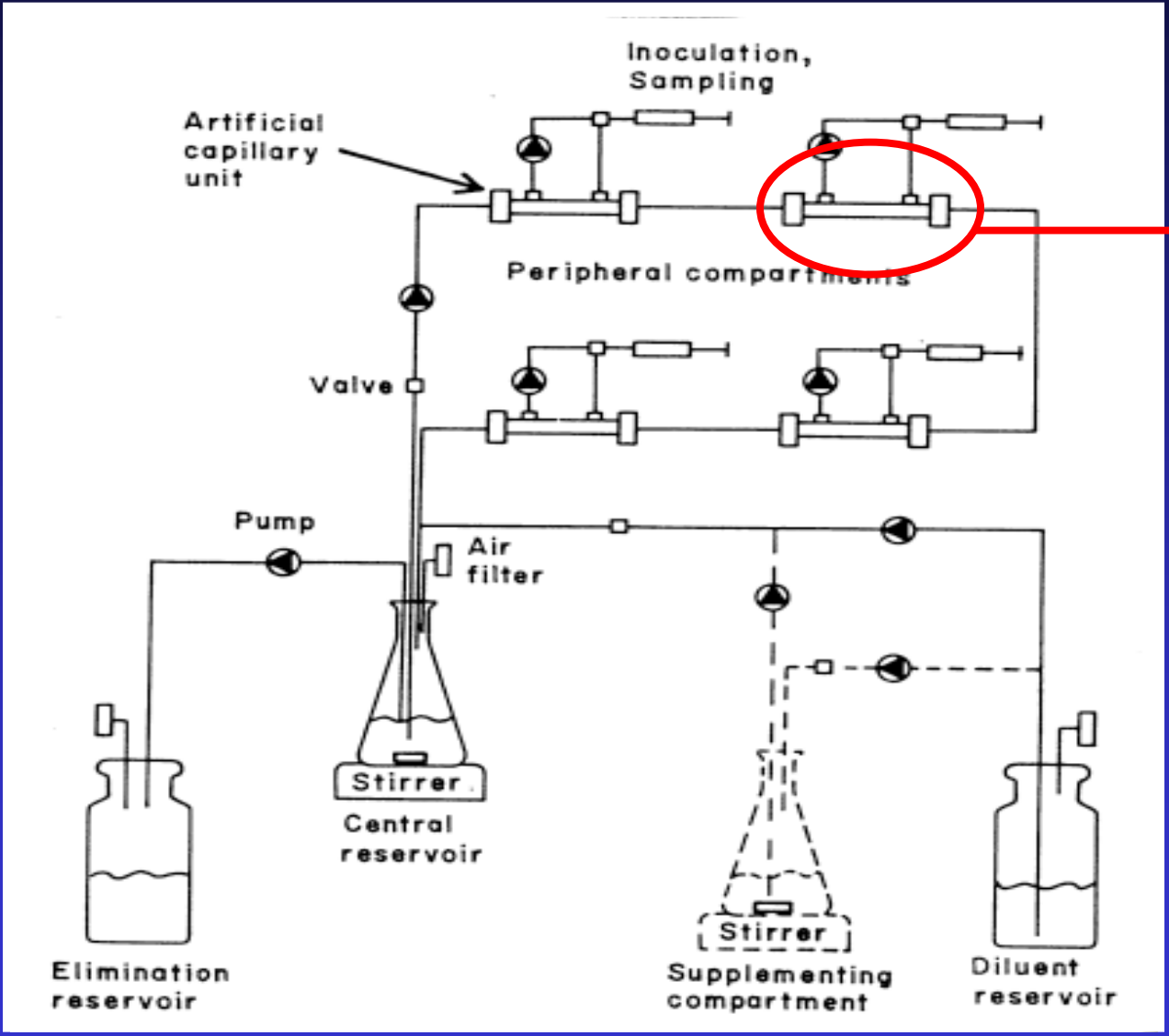
Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001

Dilution models: a simple, useful system ...



Adapted from M.N. Dudley, ISAP / FDA Workshop, March 1st, 1999

Diffusion models

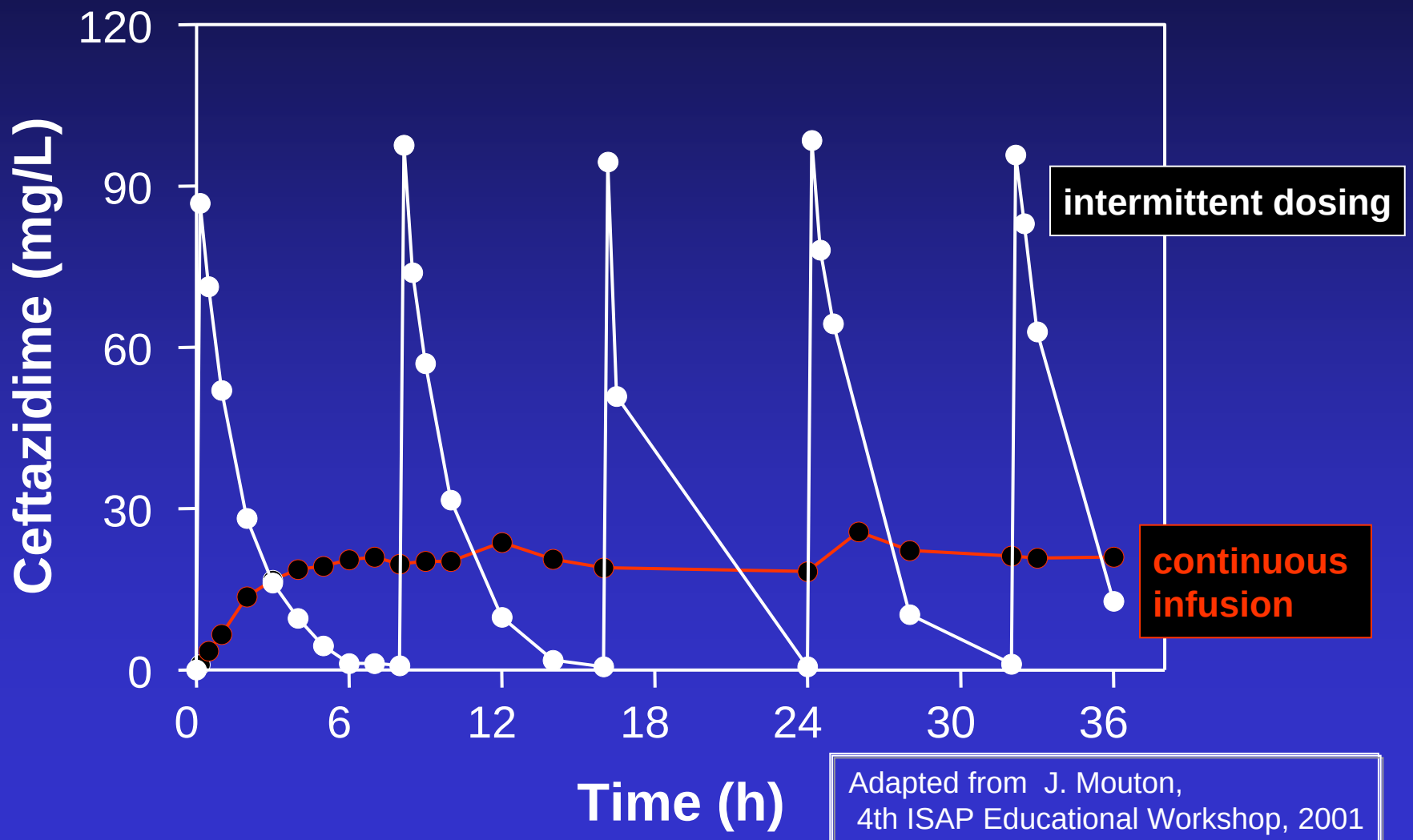


- **Membranes** (hollow fibers)
- **dialyzers** (artificial kidneys)

Adapted from M.N. Dudley, ISAP / FDA Workshop, 1999

Some models can be very complex

The goal is to mimic potentially useful and achievable serum concentration variations



Adapted from J. Mouton,
4th ISAP Educational Workshop, 2001

Why *in vitro* dynamic models ...

- **The goal is to establish basic relationships between drug exposure (PK) and effect (PD)**
  - **PK/PD parameters for efficacy to apply across species, models, for combinations, etc...**
  - **Basis of dosage in phase II trials**

- **Limitations:**
  - Experimental conditions (laboursome; contamination; …)
  - Usually only 1 or 2 days (effects 'fade' after 12-24 h)
  - absence of host factors (includ. protein binding and metabolism)
  - ...

Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001

Animal models

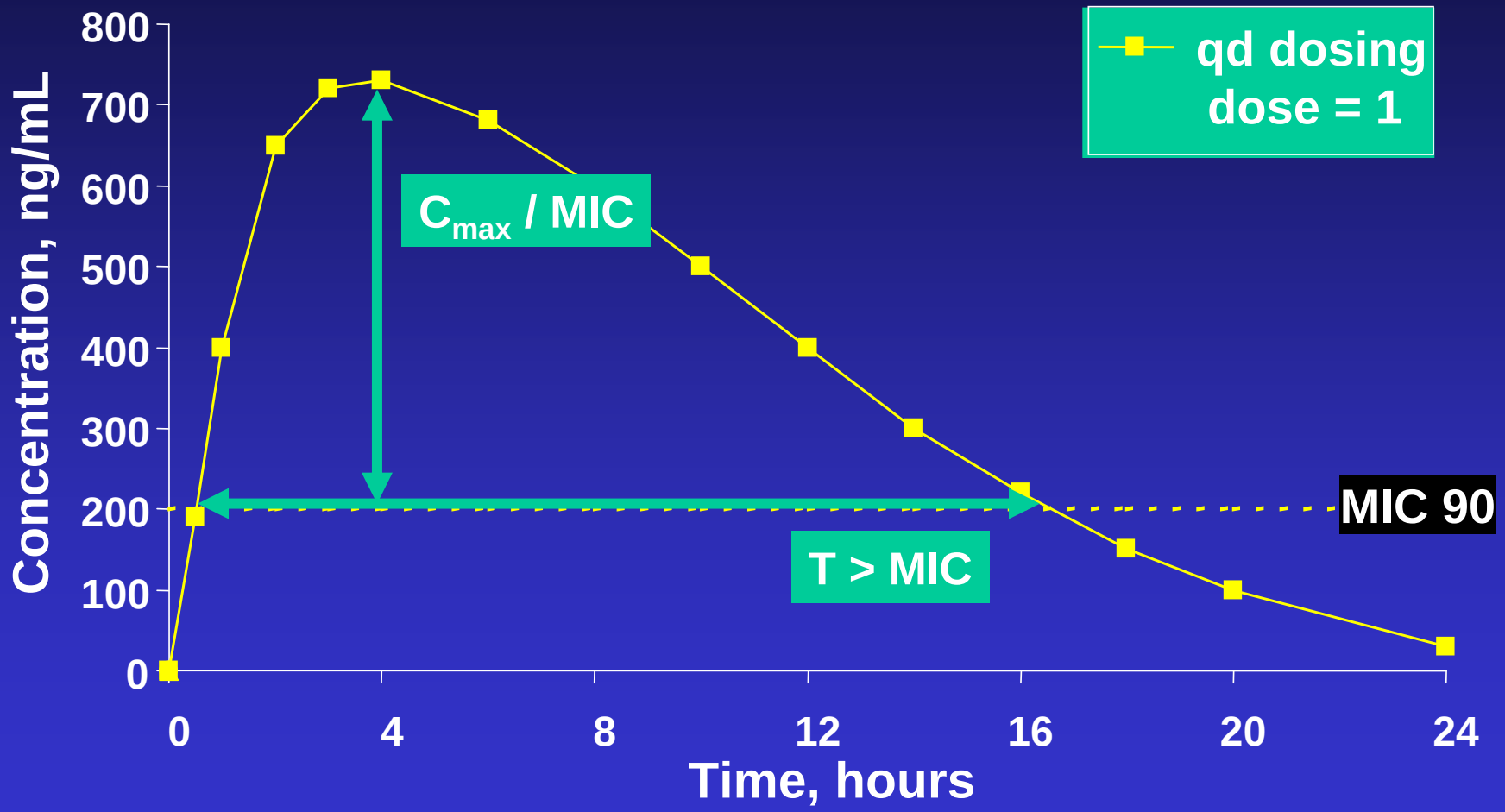
- neutropenic mouse
- rabbit (endocarditis)
- rat, guinea pig, ...

The main advantage is the possibility to explore a VERY large array of dosing regimens so as

- **dissociate PK covariables (C_{max} vs AUC …)**
- **explore the PK "conditions of failure"**

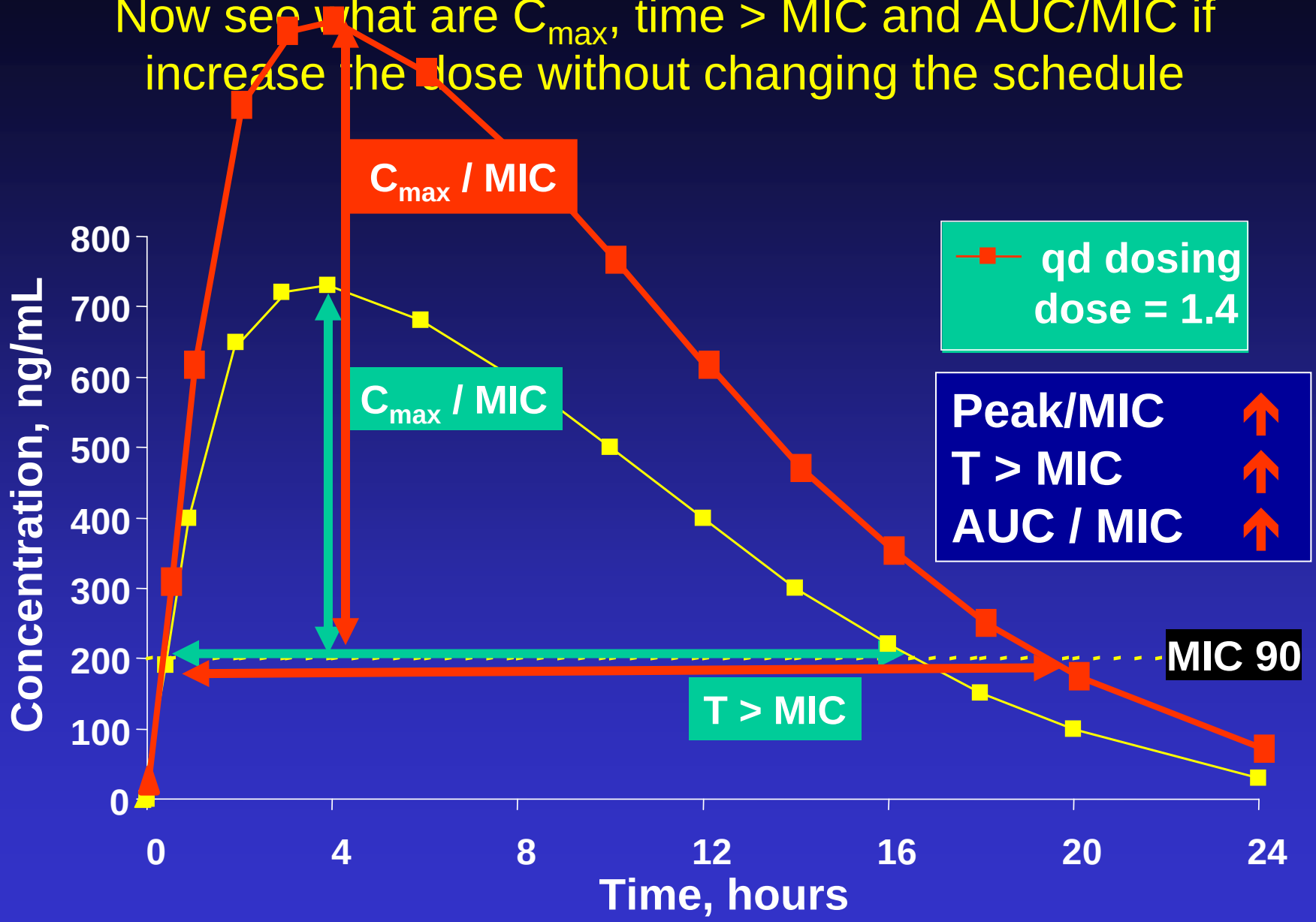
Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000

Dissociating PK covariables: see what are C_{max}, time above MIC and AUC with a once-a-day (qd) schedule of a given dose …



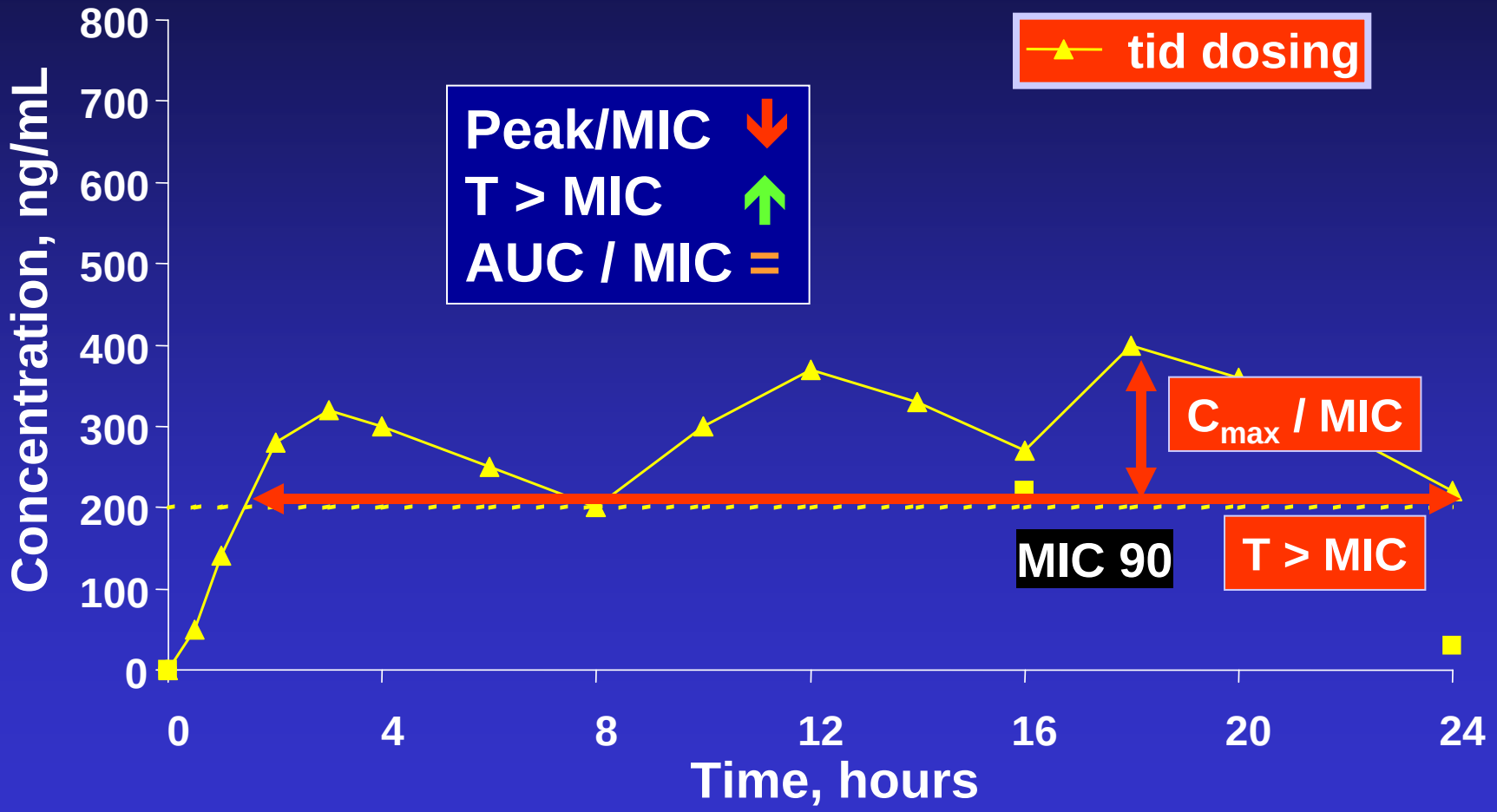
Adapted from F. O. Ajayi, ISAP-FDA Workshop, 1999

Now see what are C_{max}, time > MIC and AUC/MIC if increase the dose without changing the schedule



Adapted from F. O. Ajayi, ISAP-FDA Workshop, 1999

But see how C_{max}, time > MIC and AUC/MIC become dissociated if the SAME DAILY dose is given with a different schedule (here: divided in 3 administrations) …



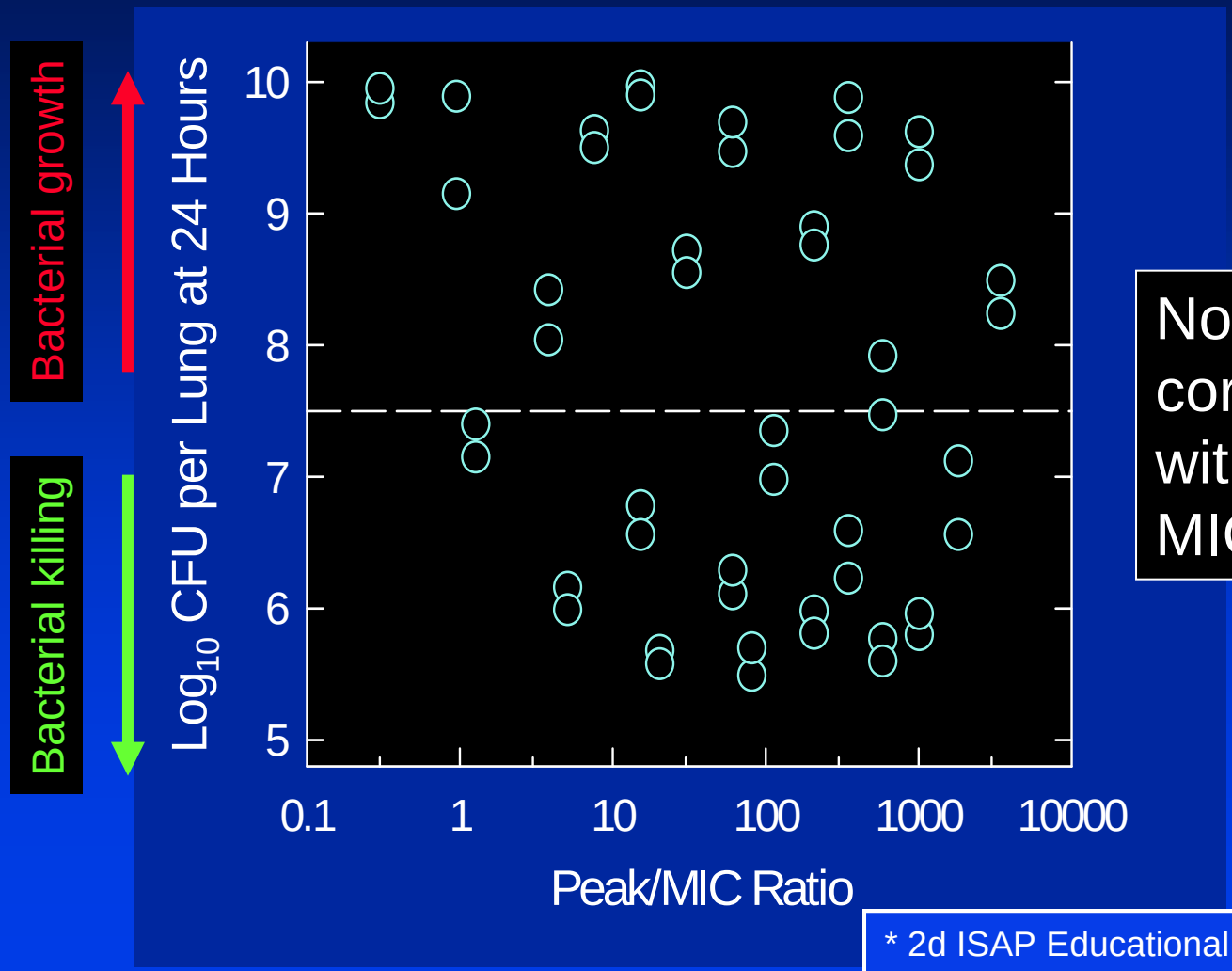
Adapted from F. O. Ajayi, ISAP-FDA Workshop, 1999

A typical animal model to establish which PK parameter is associated with efficacy

- Use neutropenic murine thigh-and lung-infection models
- Evaluate 20-30 different dosing regimens (5 different total doses given at 4-6 different dosing intervals)
- Measure efficacy from change in Log_{10} CFU per thigh or lung at the end of 24 hours of therapy
- Correlate efficacy with various pharmacodynamic parameters (Time above MIC, peak/MIC, 24-Hr AUC/MIC)

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000

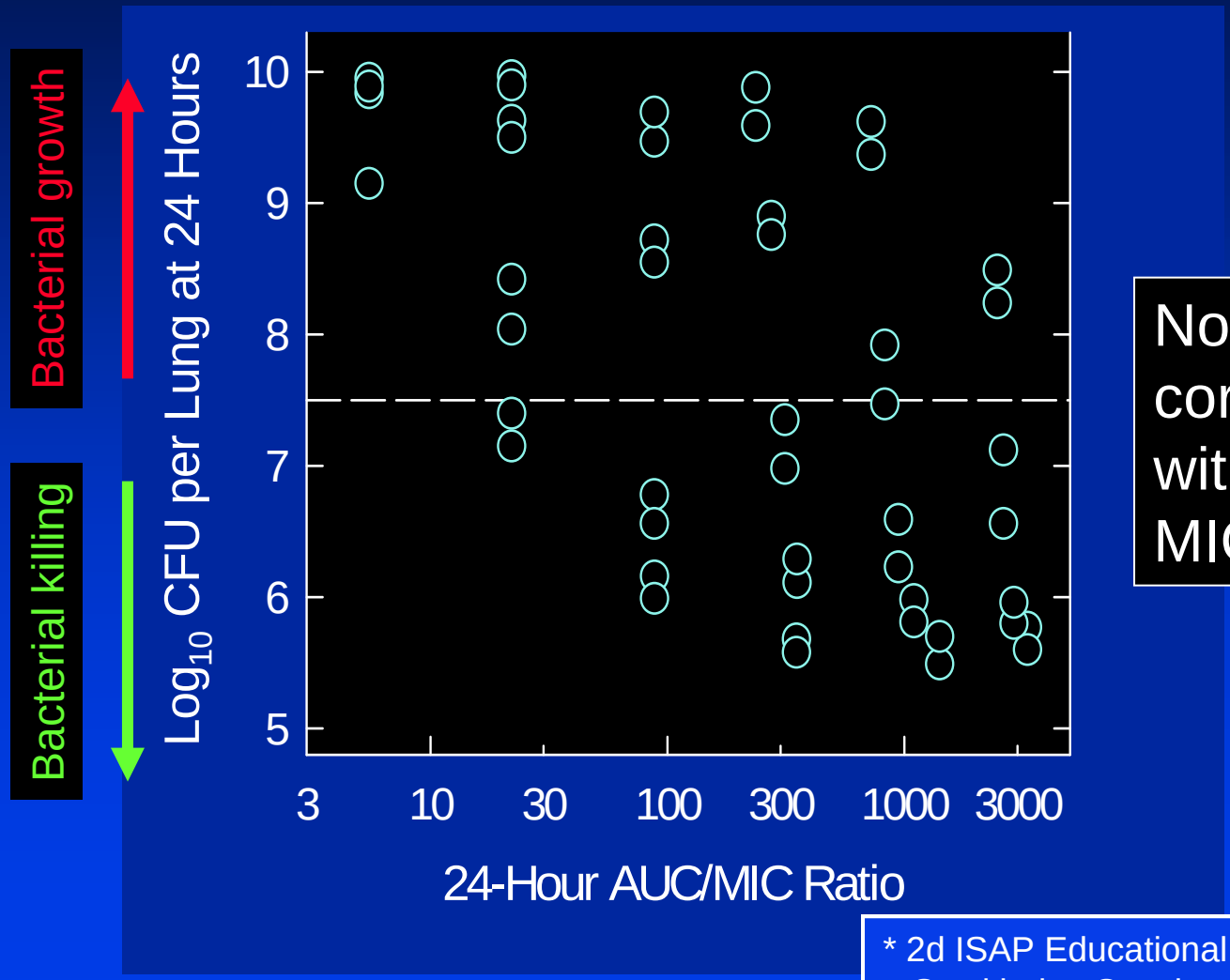
Relationship Between Peak/MIC Ratio and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)



No correlation with peak / MIC ratio !!

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

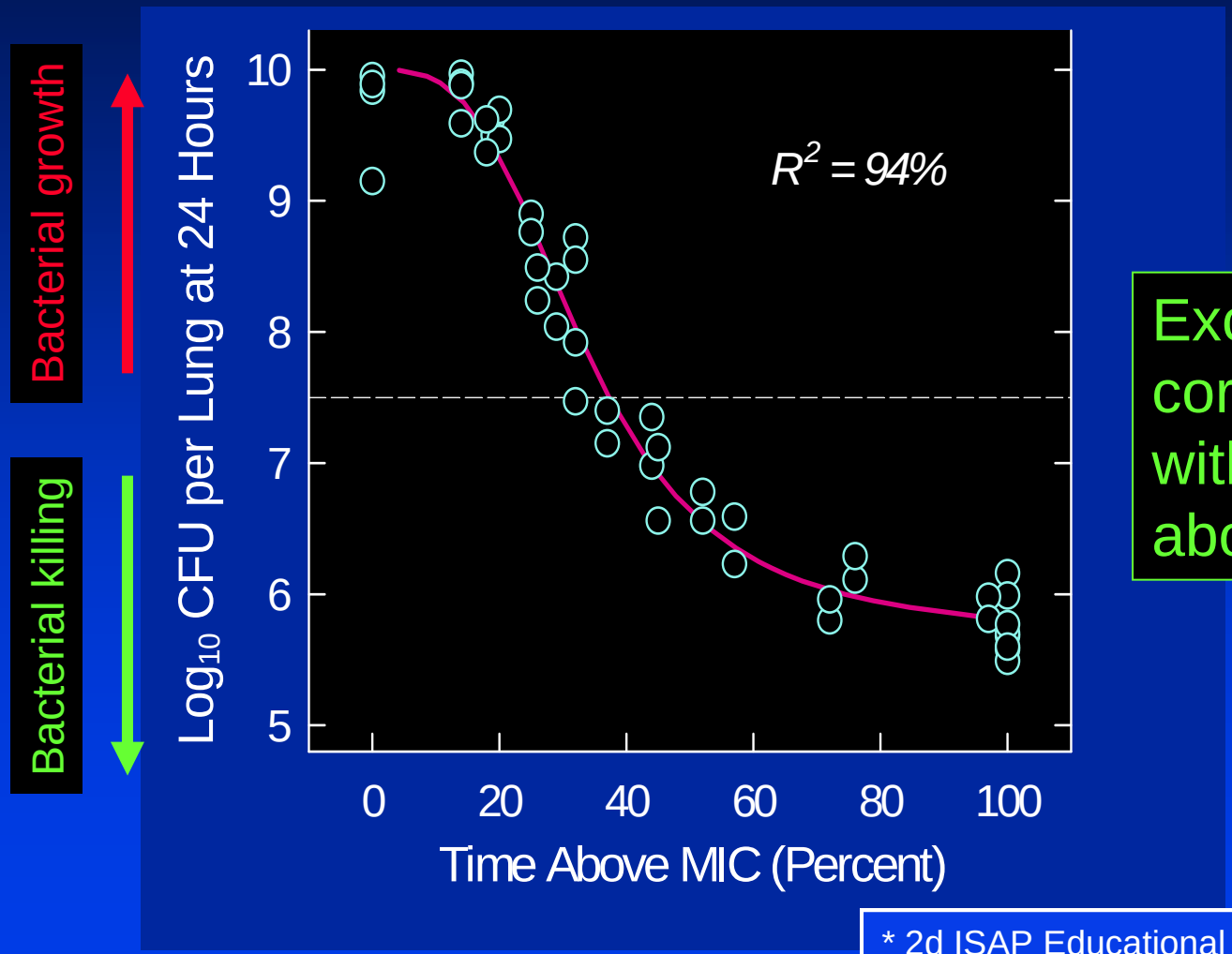
Relationship Between 24-Hr AUC/MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)



No correlation with AUC / MIC ratio !!

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Relationship Between Time Above MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)

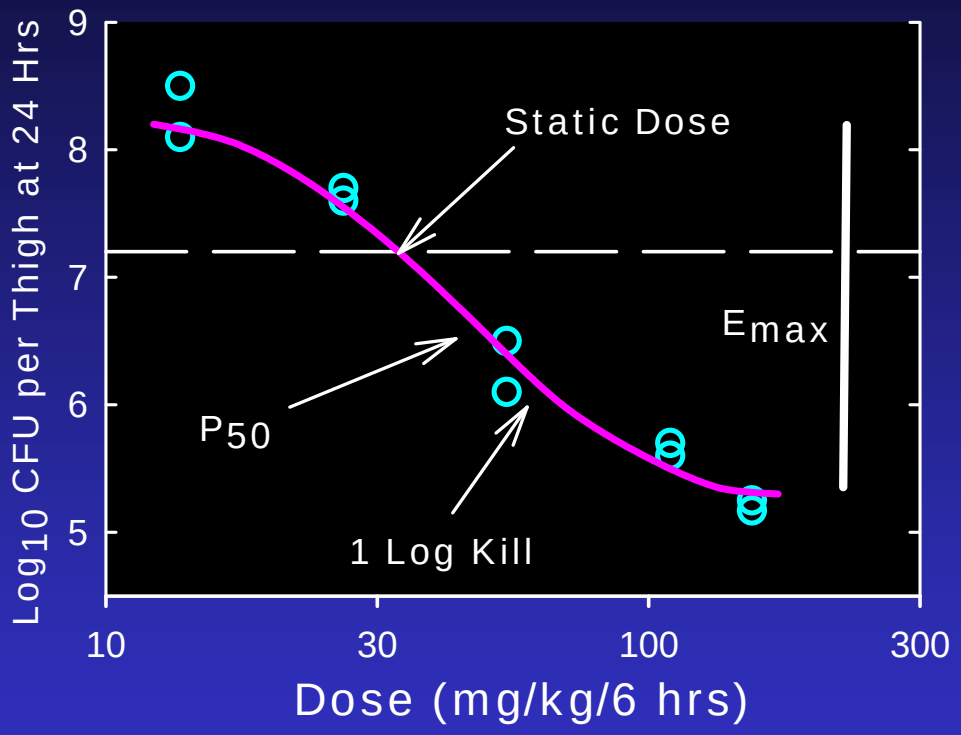


Excellent correlation with time above MIC !!

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

End-points of animal models

- Bacterial counts
  - static dose
  - 50 % effect
  - E_{max}
- Mortality
- Recovery of resistant bacteria



* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Demonstrated advantages of animal models

- **Is the magnitude of the parameter required for efficacy the same in different animal species?**

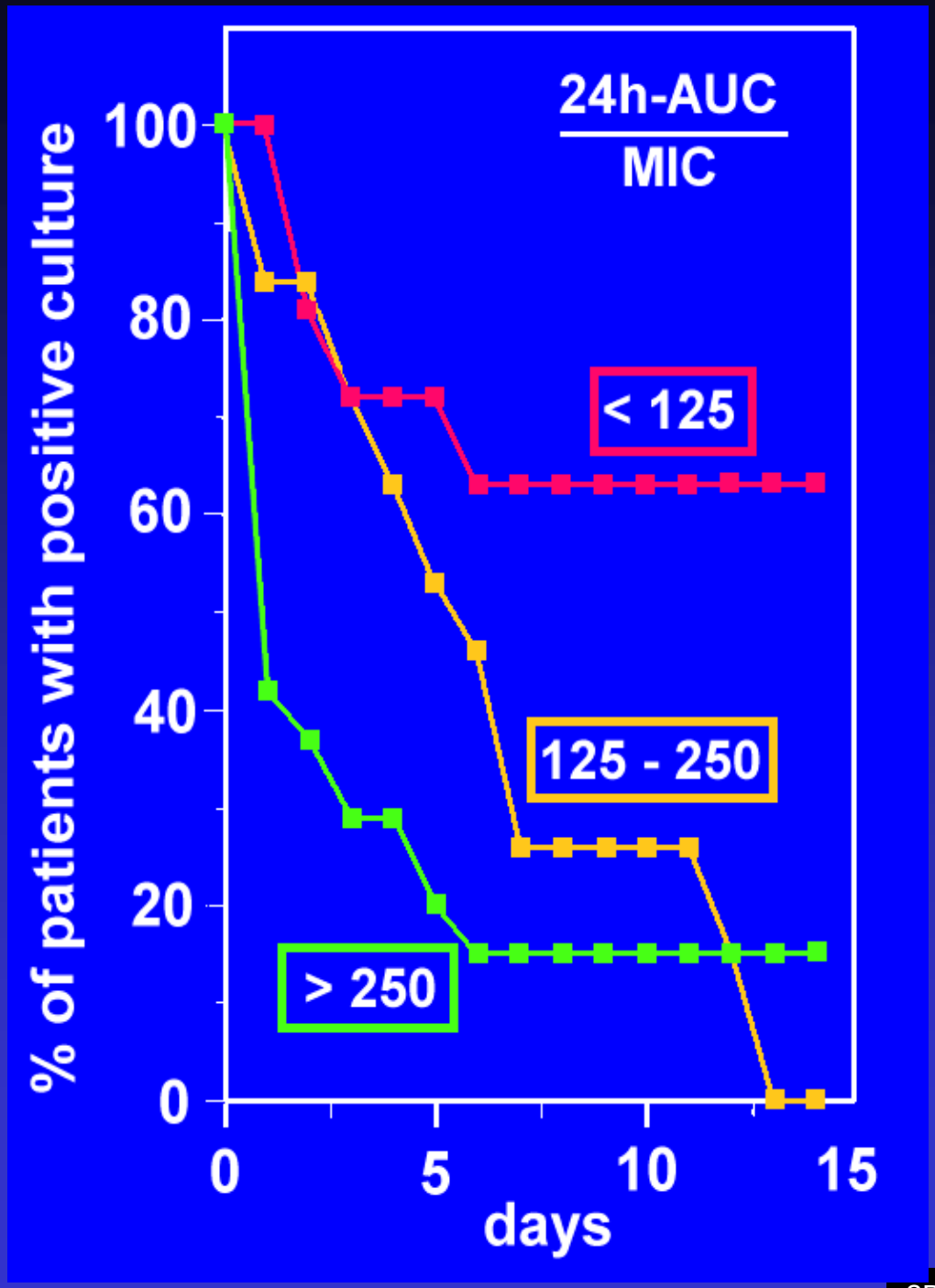
YES

- **Does the magnitude of the parameter vary with:**
  1. **the dosing regimen? NO**
  2. **different drugs within the same class? NO**
  3. **different organisms ? Minimal**
  4. **different sites of infection (e.g. blood, lung, peritoneum, soft tissue)? NO, but ...**

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000

PK/PD of fluoroquinolones in clinics

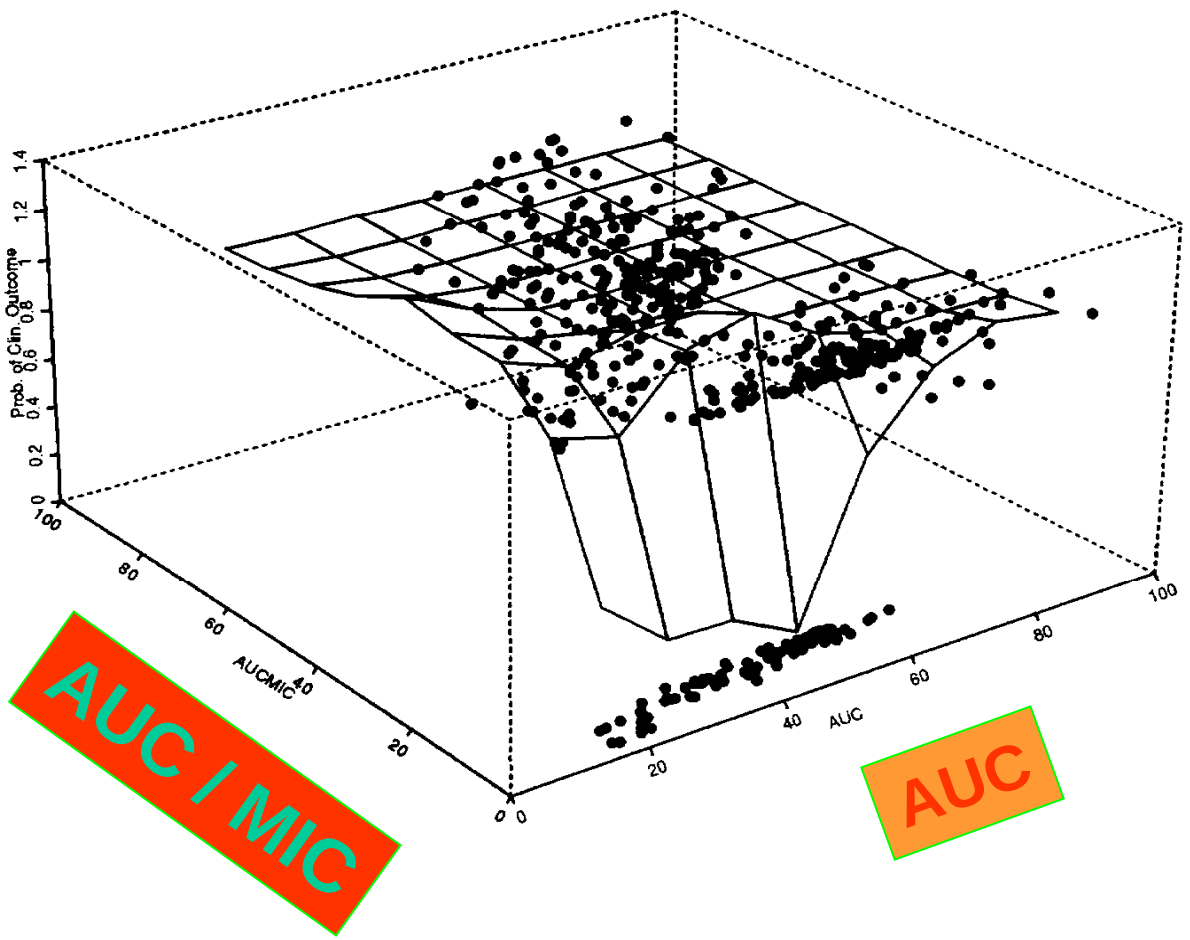
Demonstration of the role of the 24h-AUC / MIC ratio In nosocomial pneumonia



Forrest et al., AAC, 1993

Link between 24h-AUC /MIC and clinical success …

clinical outcome



F. O. Ajayi, ISAP-FDA Workshop, 1999

24h AUC / MIC : what were the data of the Forrest et al's study ?

Parameter	No.Pat.	% CureMicrob.		% CureClinical
MIC (mg/L)				
<0,125	28	82		79
0,125-0,25	13	75	succes	69
0.5	14	54		79
1	9	33	failures	44
2	2	0		0
24h AUC / MIC				
0-125	19	32	failures	42
125-250	16	81	success	88
250-1000	14	79		71
1000-5541	15	87		80

Forrest et al., AAC, 1993

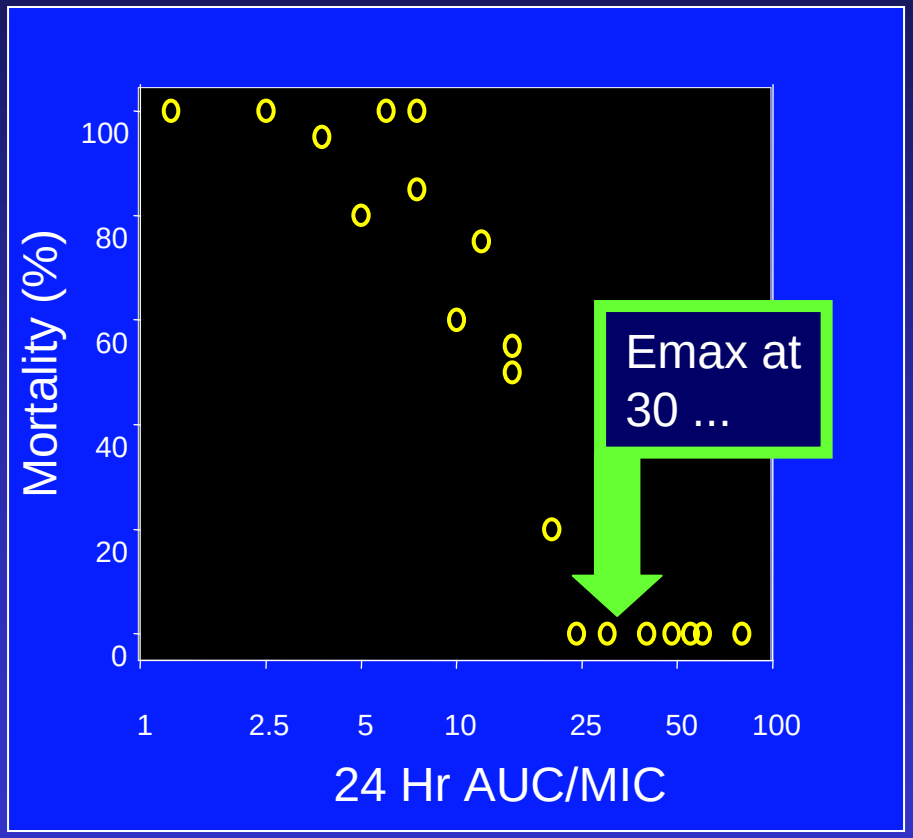
AUC/CMI =125 : a magical number??

125 was the limit below which failure rates became unacceptable based either

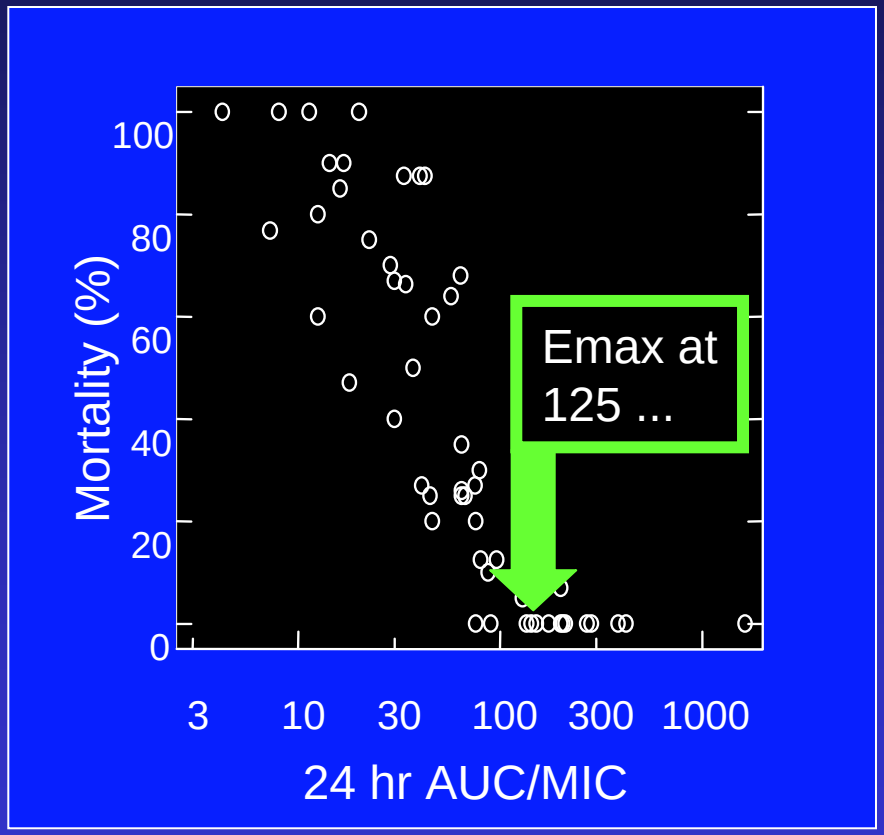
- on a large MIC
- or on a low dosage
  (AUC is proportional to the dosage)

Is 125 good for all ??

For *S. pneumoniae*, it all depends on your immune status…



non-neutropenic mice



Neutropenic mice

Why are the conclusions of the clinical trials apparently (sometimes and apparently) contradictory ?

- **insufficient separation of covariables**
  - only one or a few dosage regimens
- **not enough true failures**
  - Pathologies pas assez sévères
  - study design
- **intercurrent variables influencing outcome and not recognized as such**
- **unsufficient or inappropriate collection of PK data**
  - only “peaks” or troughs...

Correct but uncomplete conclusion

No conclusion possible

Conclusions of poor value (shed confusion…)

Population approaches : Doctor or Regulator ?

- In clinical therapy, we would like to give optimal dose to each individual patient for the particular disease

  → **Individualized therapy**

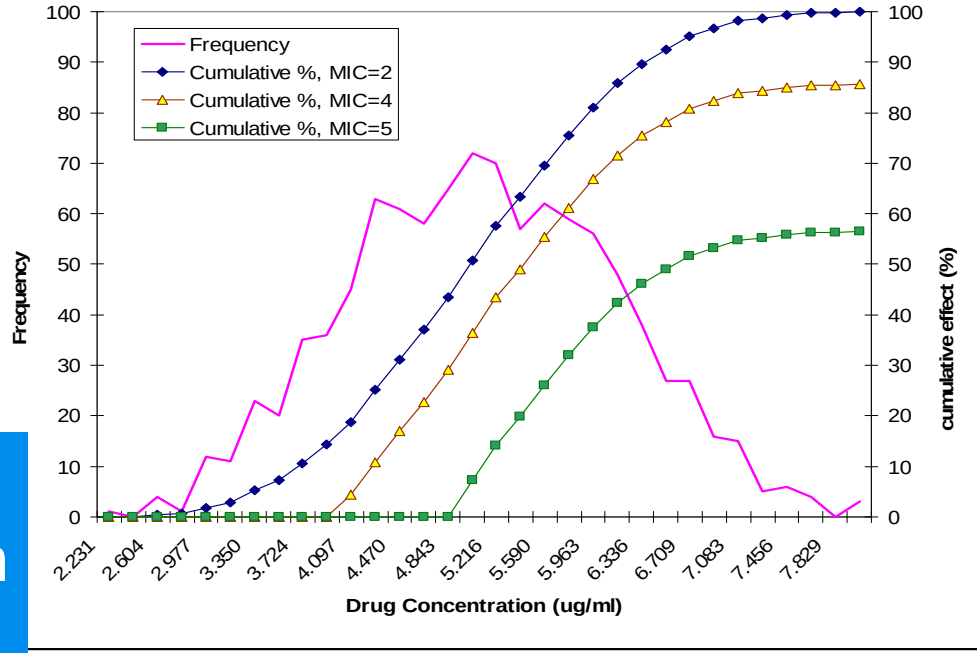
- In new drug assessment / development, we would like to know the overall probability for a population of an appropriate response to a given drug and proposed regimen

  → **Population-based recommendations**

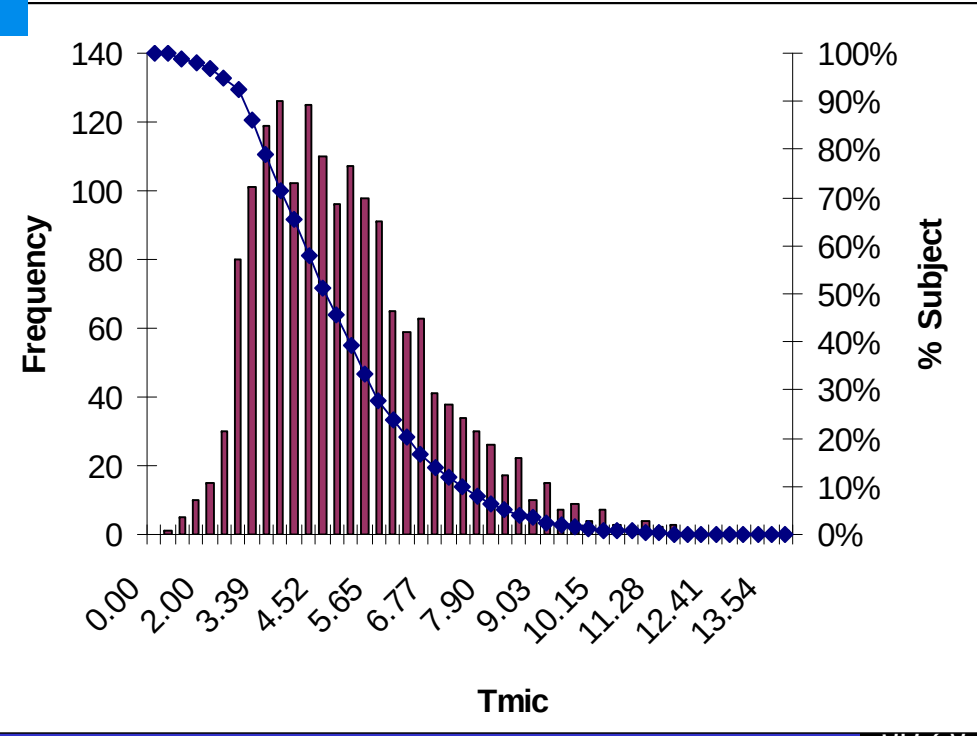
H. Sun, ISAP-FDA Workshop, 1999

Obtaining population cumulative frequencies

Quantal drug concentration effects



Quantal T>MIC plots



H. Sun, ISAP-FDA Workshop, 1999

“Monte Carlo” simulations

Monte Carlo Simulation : the basics …

- "randomly" generating at least 10,000 scenarios of PK and PD parameters that could be seen in patients
- Determining what the PK/PD values would be under each of the 10,000 scenarios
- Forming a histogram of those results. This represents a discrete approximation for the probability distribution of the data.

➢ Monte Carlo simulation allows us to make use of prior knowledge of how a target population handles a specific drug to predict how well that drug will perform clinically at the dose chosen for clinical trials

Monte Carlo Simulation …

How is this done?

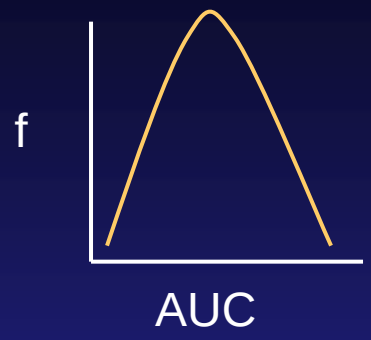
- Through use of data from a population PK study, a sampling distribution is set up

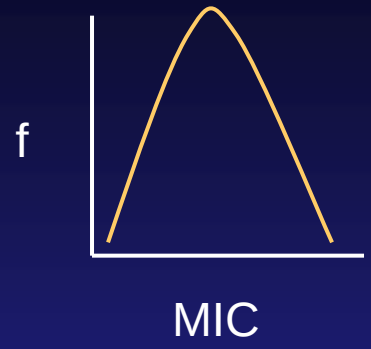
think of every body in the world in a bucket from which you randomly select a large number of subjects, each of whom knows their PK parameter values.

- This allows the pertinent PK parameters to be calculated for all the subjects
- you then only need to apply your pertinent PD parameter !!

Modified from:
G. Drusano, Joint ISAP/ECCMID Symposium, Glasgow, UK, May 11th, 2003

“Monte Carlo” simulation for pneumococci (based on AUC/MIC)

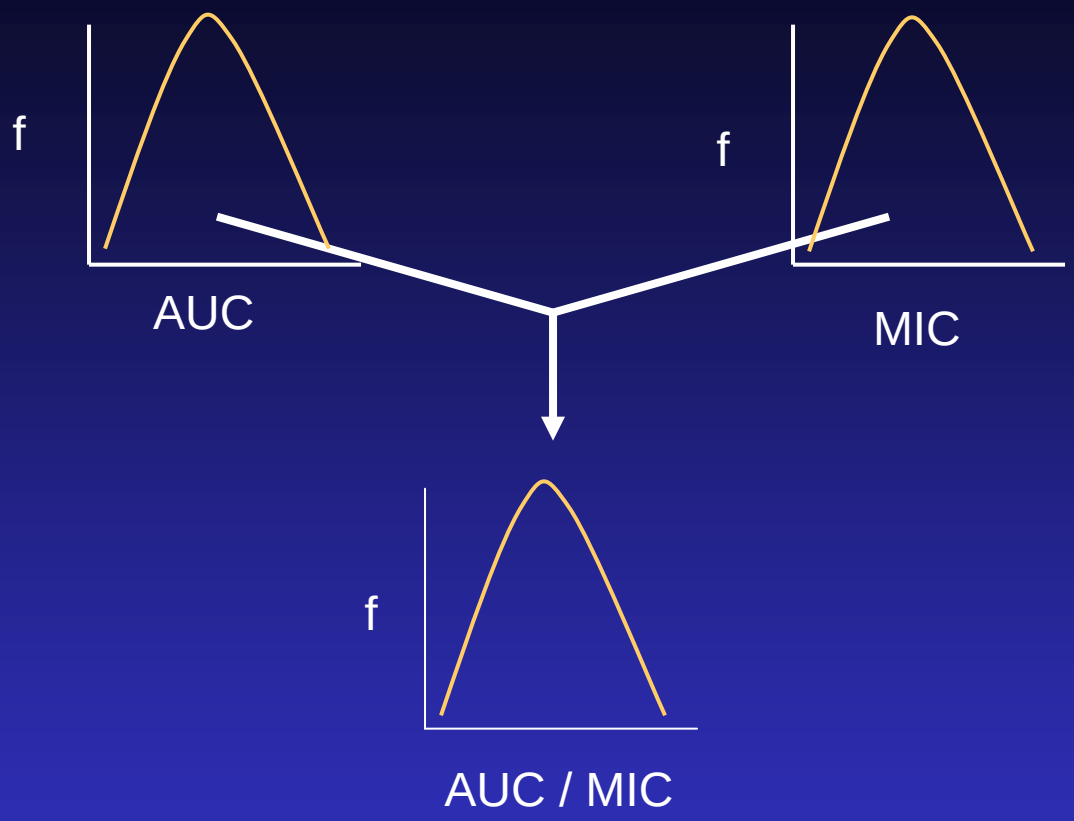




1. Patients' PK distribution

2. Bacteria MIC distribution

“Monte Carlo” simulation for pneumococci (based on AUC/MIC)

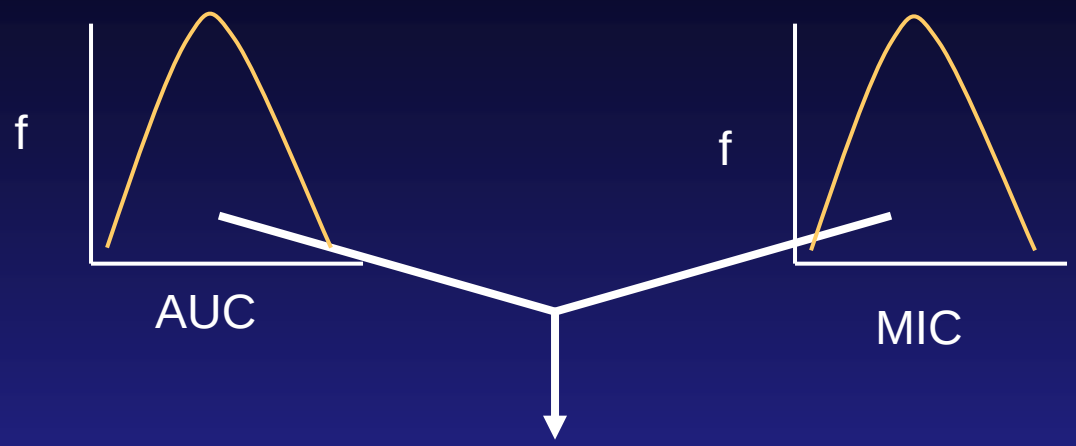


patients

broth

3. Simulated AUC/ MIC distribution

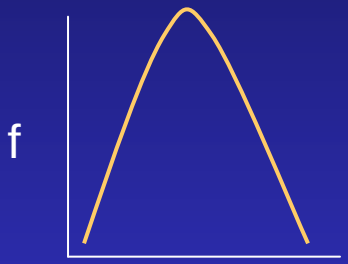
“Monte Carlo” simulation for pneumococci (based on AUC/MIC)



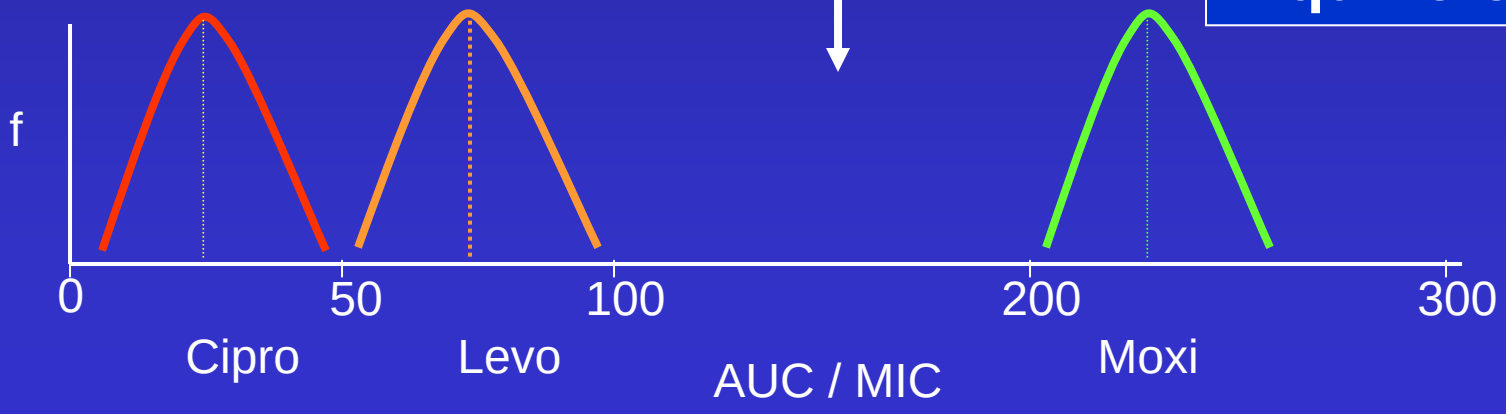
1. patients

2. broth

3. Simulation …

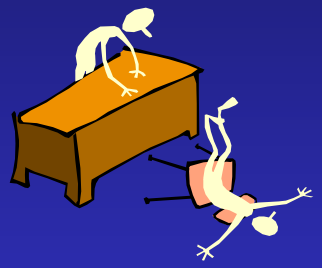


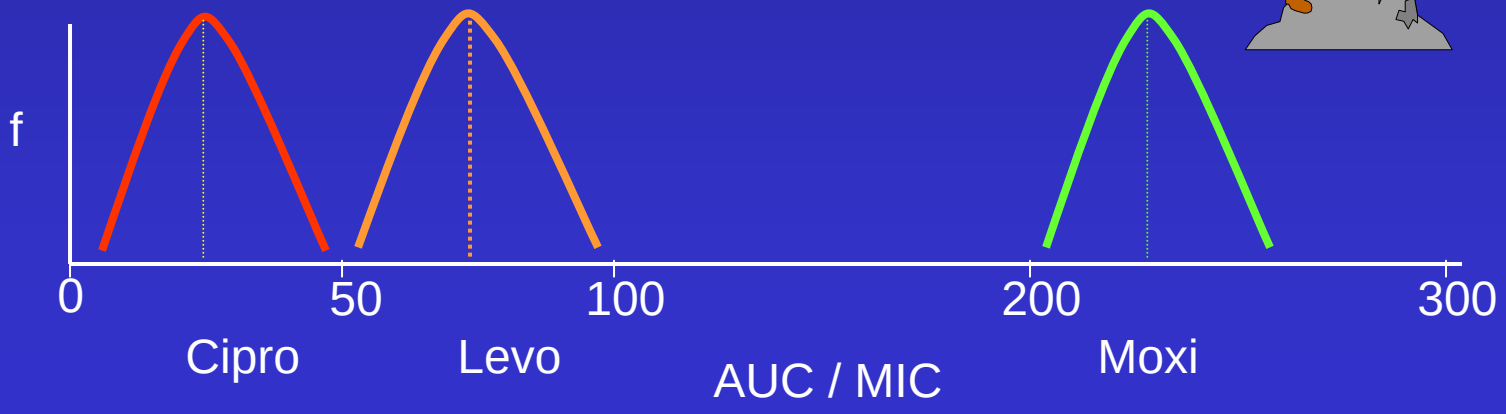
4. Solve the equations for the AUC values of 3 quinolones …



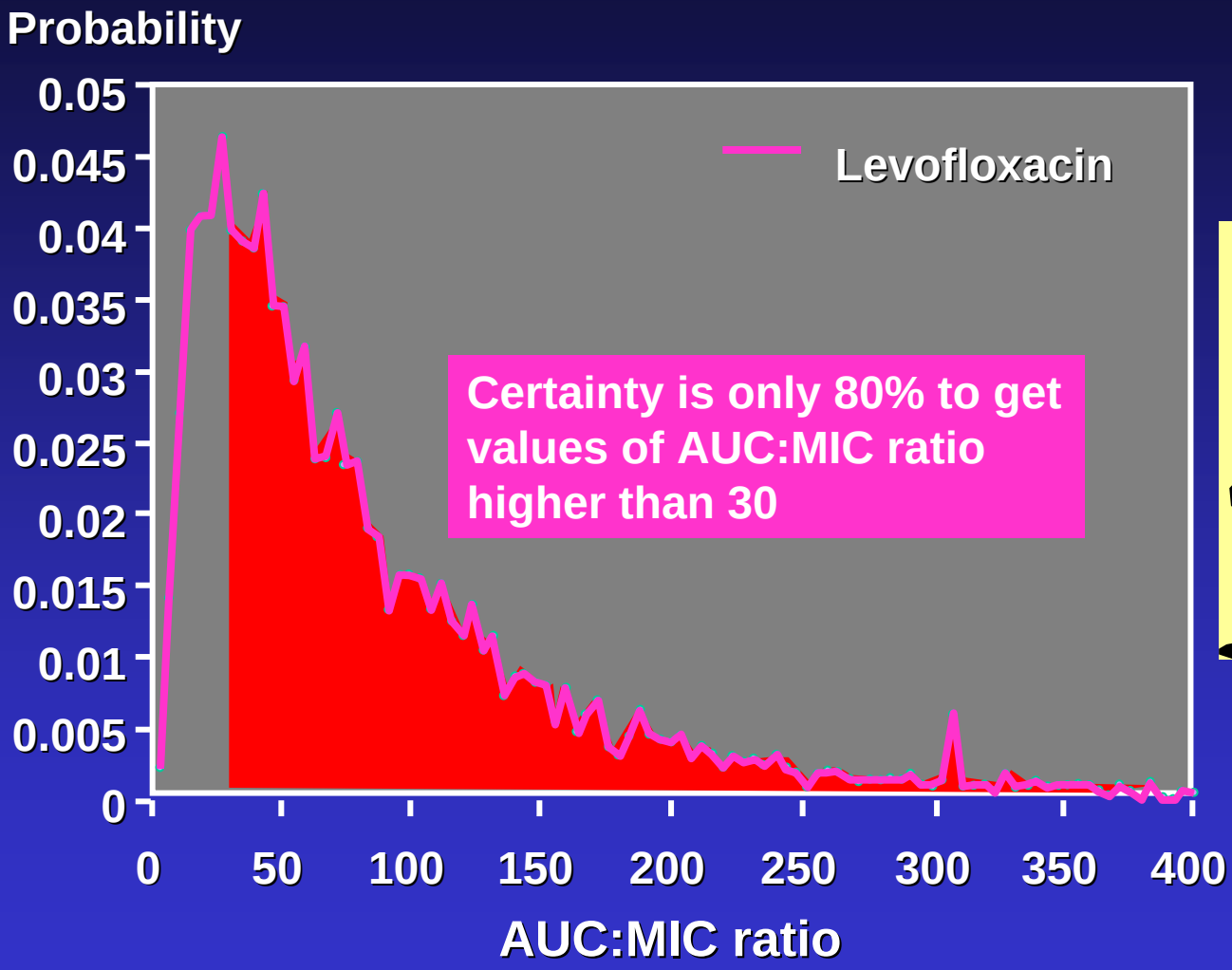
“Monte Carlo” simulation for pneumococci (based on AUC/MIC)

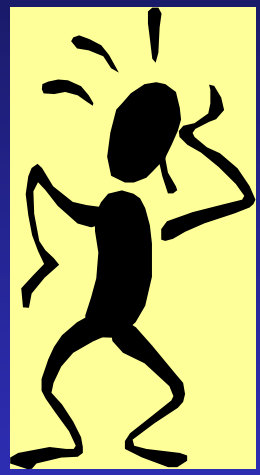
The results are obvious …





Another look at Monte-Carlo simulations : Levofloxacin Vs *S. pneumoniae*

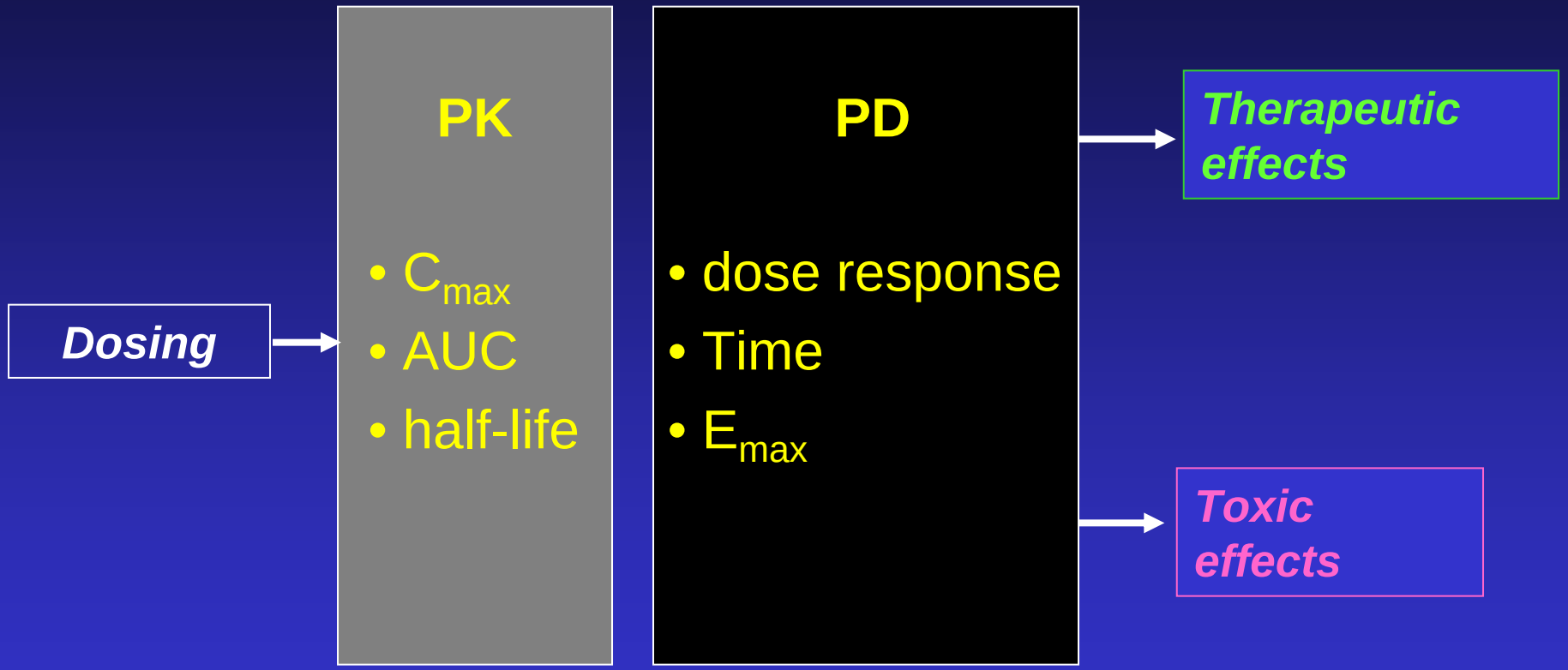




Preston SL, Drusano GL et at. AAC 1998;42:1098-1104; Ambrose PG, Grasela D. ICAAC 1999

Ambrose PG et al Chapter 17 in Antimicrobial Pharmacodynamics in Theory and Clinical Prectice, eds Nightingale CH, Murakawa T, Ambrose PG. 2002. Marcel Decker, NY

Those methods allow
to know that
for each antibiotic



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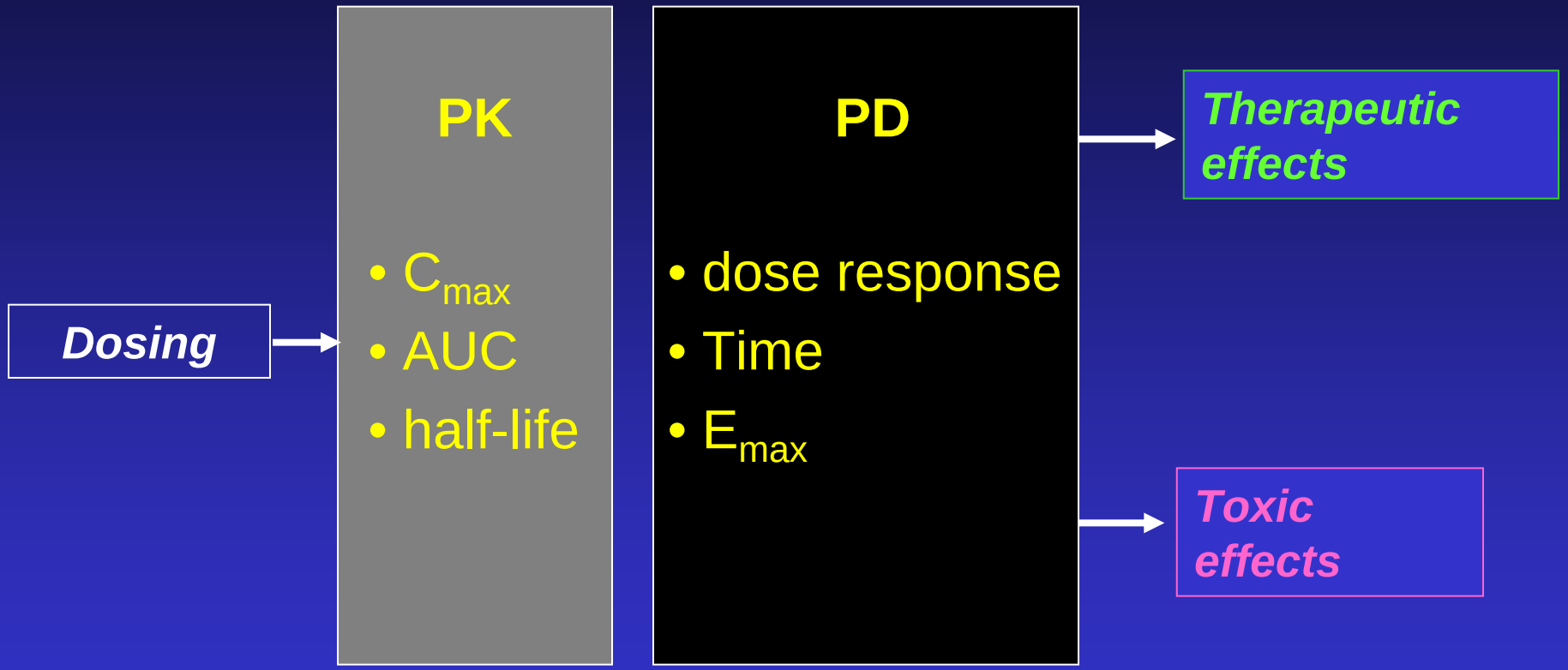

We now will tell you what these methods show ….

Section 3 c