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Introduction to Pharmacokinetics/Pharmacodynamics: PK and PD Models

Ahmed A Abulfathi

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Even water has a toxic dose

What is the dose-concentration-effect relationship? How does it evolve with time?

"All things are poison, and nothing is without poison;
only the dose permits something not to be poisonous."
Paracelsus (1493-1541)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hyponatremia among Runners in the Boston Marathon

Christopher S.D. Almond, M.D., M.P.H., Andrew Y. Shin, M.D.,
Elizabeth B. Fortescue, M.D., Rebekah C. Mannix, M.D., David Wypij, Ph.D.,
Bryce A. Binstadt, M.D., Ph.D., Christine N. Duncan, M.D.,
David P. Olson, M.D., Ph.D., Ann E. Salerno, M.D.,
Jane W. Newburger, M.D., M.P.H., and David S. Greenes, M.D.

Therapeutic relevance of PK/PD

- Patients with Diabetes, HIV and certain cancers, versus those with occasional headache
- The duration of therapy is usually between these extremes
- Dosage regimen?
- Therapeutic objective
- Because all drugs have untoward effects, successful therapy depends on balance between desirable and undesirable effects

Achieving optimal therapy requires the appropriate drug of choice

- Then the questions:
  - How much?
  - How often?
  - How long?
  - Which route? And
  - Which dosage forms?

Learning objectives

- Revise meaning of pharmacokinetics (PK) and pharmacodynamics (PD)
- Understand the biological basis of PK and PD models

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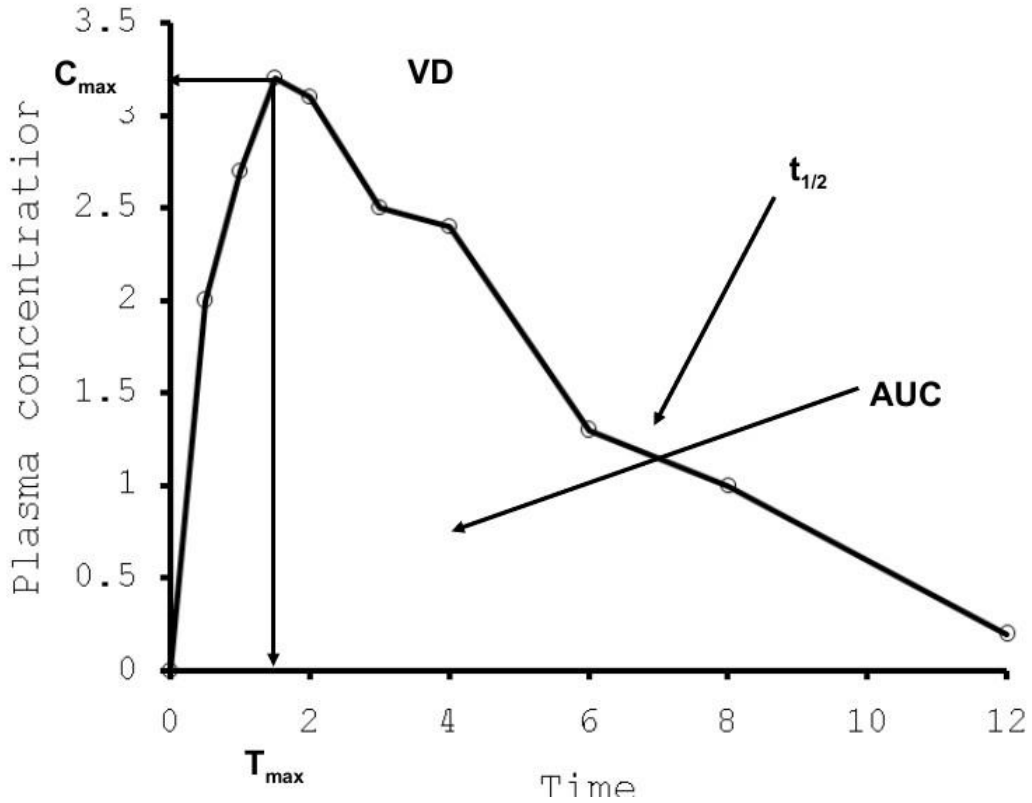
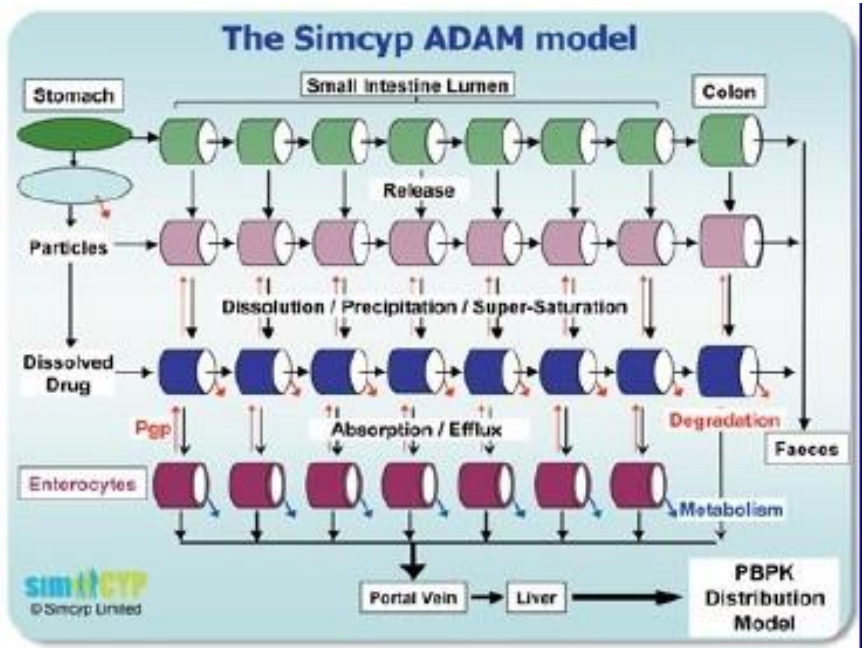
Pharmacokinetics: “What the body does to the drug”

- Typical data arising from a PK study: concentration *vs* time
- How do we interpret these data?
- Descriptive analysis: *AUC*, C_{max}, t_{max}, elimination half-life ($t_{\frac{1}{2}}$)
- Mathematical model: n. a description or representation of something conceived or presented in mathematical terms. (OED)

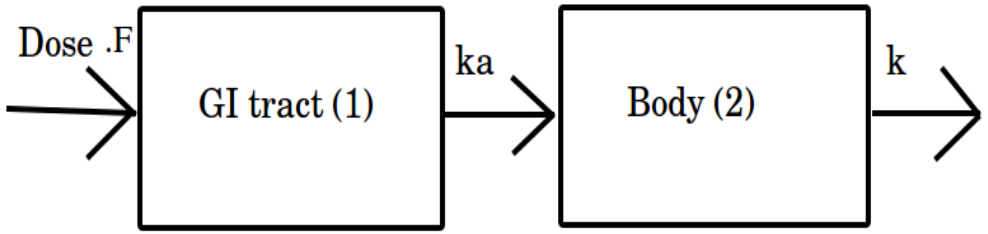


Pharmacokinetic models

Derive model from components of the system, then simulate expected PK:

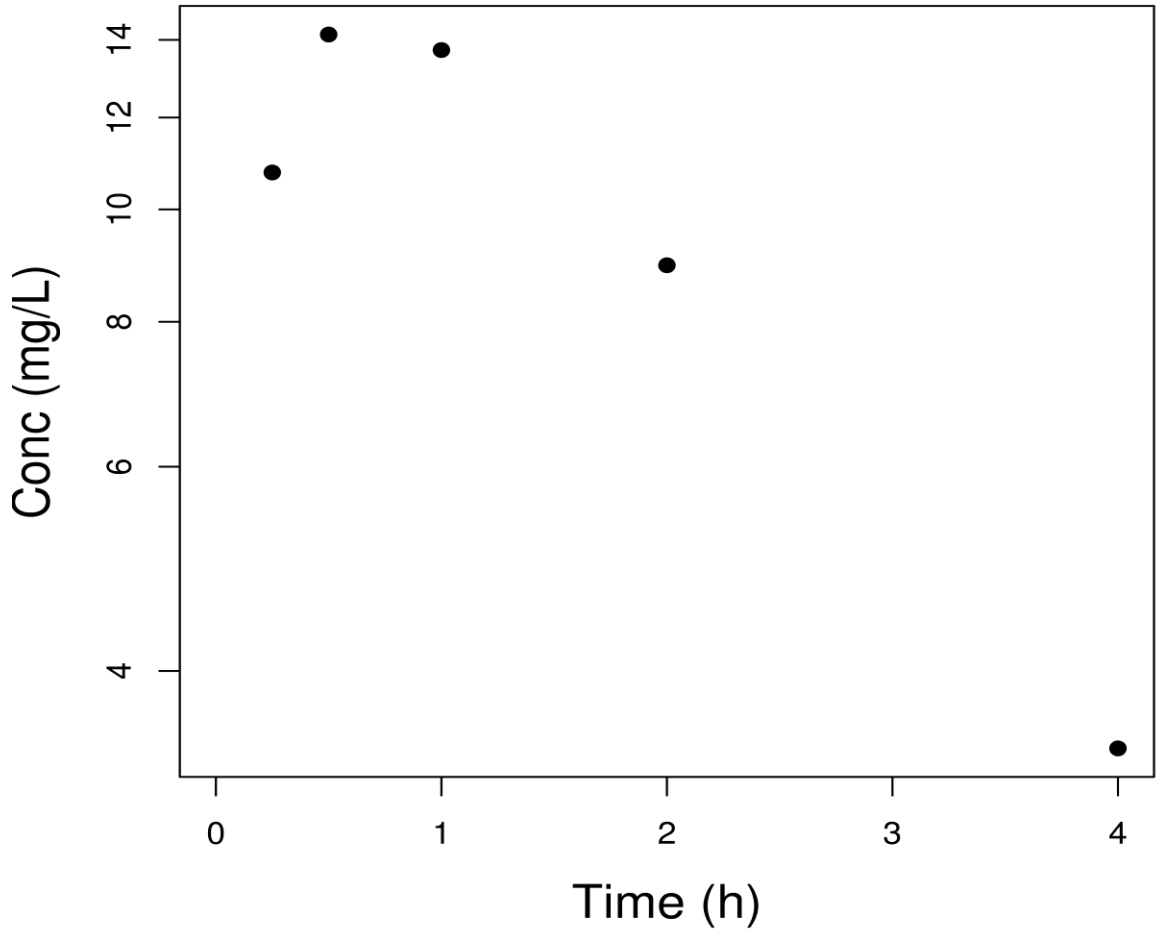


Estimate model parameters from observed data (the main focus of this course)



Pharmacokinetics: Some data transformed

Transformations?



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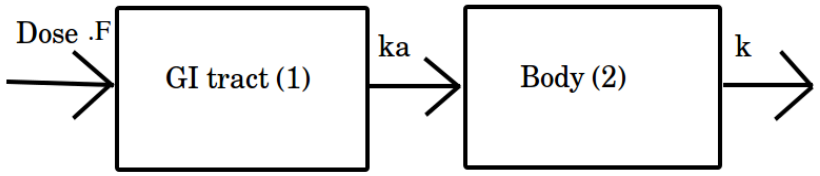
Pharmacokinetics: One-compartment extra vascular administration mathematical model



$$C(t) = \frac{Dose \cdot k_a}{V \cdot (k_a - k)} \cdot (e^{-k \cdot t} - e^{-k_a \cdot t}),$$

$$k = \frac{CL}{V}.$$

- Mathematical model: equation describing observed trend (usually nonlinear)
- Takes known information (covariates) assumed to be measured *without error*: e.g. Dose, time
- We want to find (estimate) best values of *parameters* to fit observations
- Use models with parameters (e.g. *CL*, *V*) that have biological meaning

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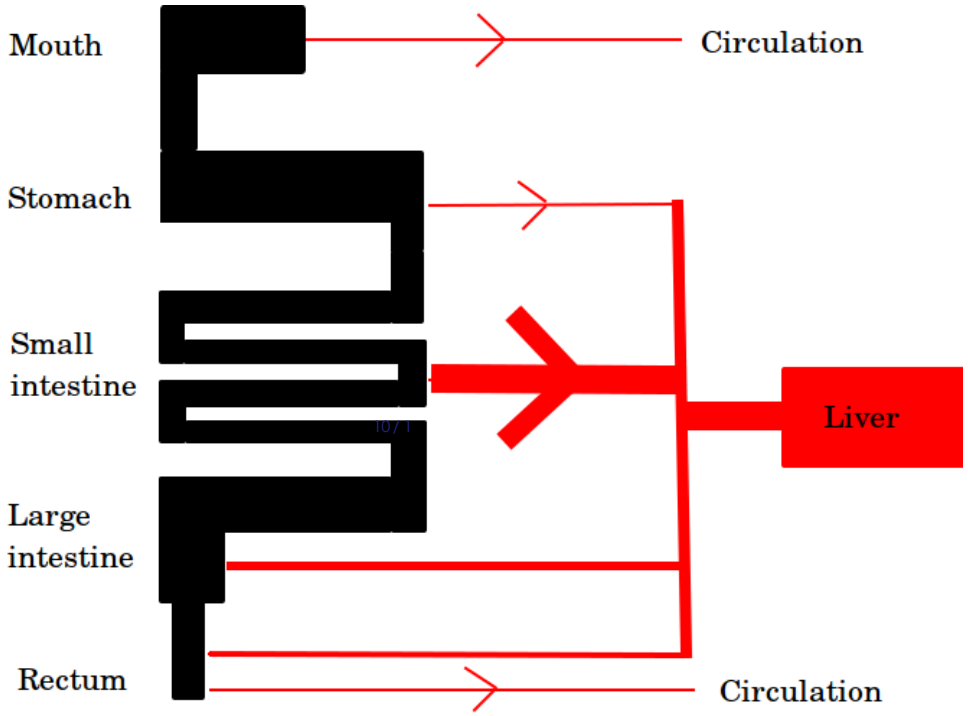
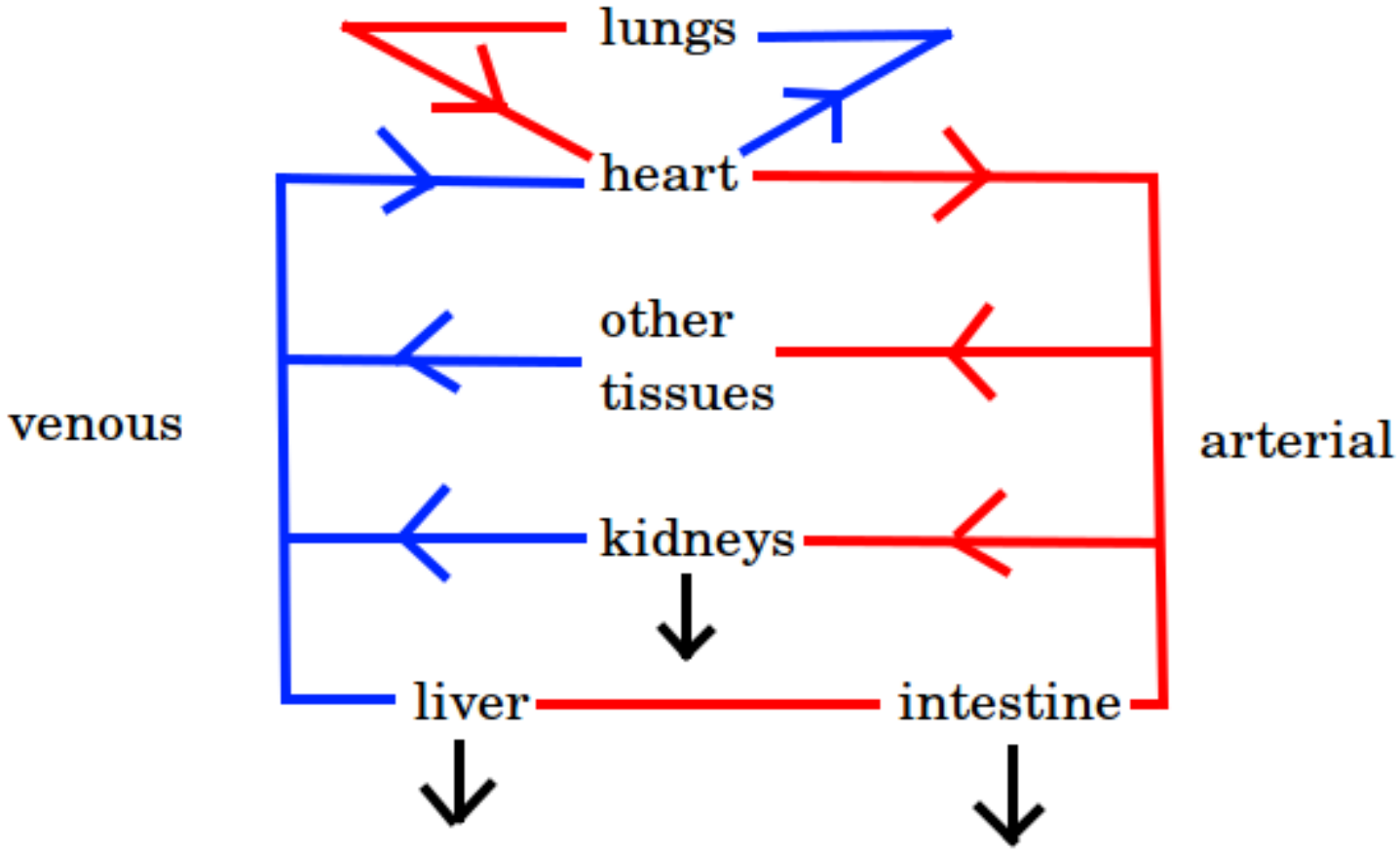
Biological basis: Absorption



Bioavailability $F \in [0, 1]$

$F = Fa \cdot Fg \cdot Fh$

Biological basis: Distribution



Biological basis: Distribution

Physiological basis of volume of distribution for a 70 kg adult:

- Total body water: 41 L
  - Intracellular: 23 L
  - Extracellular: 18 L
- Extracellular water further partitioned to:
  - Plasma water 3 L
  - Interstitial water 15 L

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A drug's physicochemical properties can determine its distribution

- Hydrophilic drugs and highly charged drugs cannot cross membranes → $V < 41L$
- Lipophilic or uncharged drugs can often have $V >> 41L$
- Protein binding can limit distribution: albumin, lipoproteins, immunoglobulins, erythrocytes and α_1 acid glycoproteins

- Only free drug is availabile for pharmacological action

Biological basis: Metabolism

- Major sites: LIVER, gi tract
- Minor sites: kidneys, lungs
- Enzymatic reactions: make things more water soluble
- Phase I: Cytochrome P450 (e.g. CYP3A4, CYP2D6)
- Phase II: Multiple (e.g. UGT)

Well-stirred liver model:

$$E_R = \frac{CL_I}{Q_H + CL_I},$$
$$CL_H = Q_H E_R.$$

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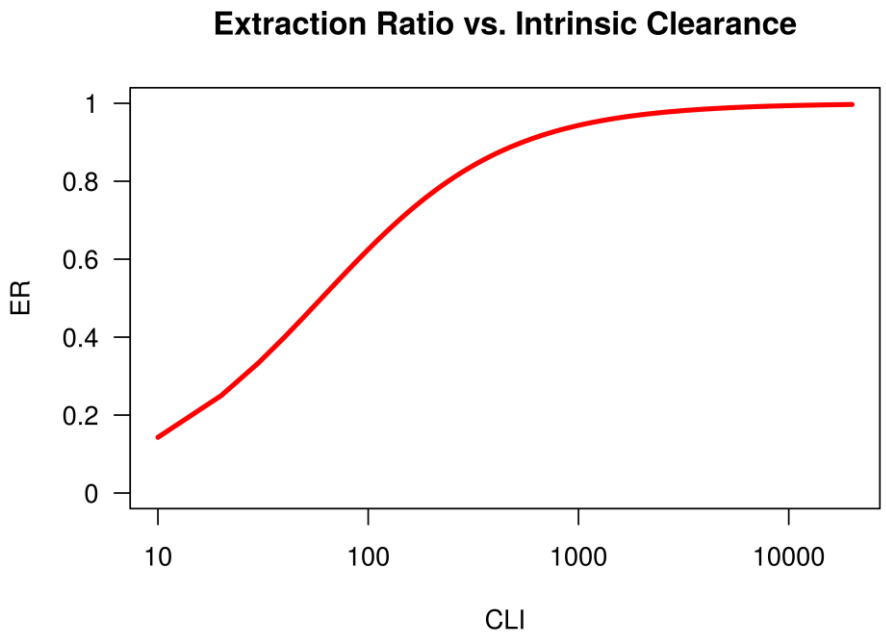
Hepatic metabolism mechanistic basis

Well stirred model of hepatic clearance (assume fub=1):

$$E_R = \frac{CL_I}{Q_H + CL_I},$$
$$CL_H = Q_H E_R.$$



- $CL_I \propto$ enzyme abundance
- Enzyme abundance $\propto$ liver volume (scales with body size)
- Hepatic blood flow (scales with body size)
- Maturation or genetic polymorphisms may change E_R

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Clearance is one of the most important PK parameter

Very important concept in PK. V and CL referred to as primary PK parameters, from which secondary parameters (AUC, $t_{1/2}$) calculated

- Clearance: The volume cleared of drug per unit time, e.g. L/h
- Elimination depends (at least partly) on flow to eliminating organs, in volume per time, CL is a flow parameter
- Elimination rate constant $k = CL/V$, units time^{-1}
- Total CL given by sum of CL from each route e.g. total clearance = renal clearance + hepatic clearance
- CL determines AUC ($AUC = dose/CL$)
- CL determines concentration at steady-state C_{ss} ($C_{ss} = doserate/CL$)

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Summary of PK

Very important to understand this:

1. Give a dose (amount)
2. Volume of distribution used to transform to a concentration, and scales with physiological volumes
3. Clearance (in volume/time) determines exposure and links with biology (e.g. blood flows, glomerular filtration)
4. Elimination rate constant can be derived from *CL* and *V* but should not be estimated from data if one wants to incorporate biological prior knowledge into the model

Some important relationships:

- Steady-state concentration $Css = Doserate/CL$
- Average concentration $Cave = AUC(0-t)/t$
- $AUC = \frac{D}{CL}$
- $k = CL/V$

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Pharmacodynamics

- "What the drug does to the body"
- PD (drug effect) needed to define dose
- PD endpoints vary widely:
  - Measured biomarker
  - Diseases score
  - Clinical endpoint/event
- Fundamental underlying relationship of drug binding to receptor causing response (effect)

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Biological basis: Pharmacodynamics

Law of mass action: Drug (D) combining with Receptor (R)

$$[D] + [R] \leftrightarrow [DR], \quad (5)$$

$$[DR]k_{off} = [D][R]k_{on}. \quad (6)$$

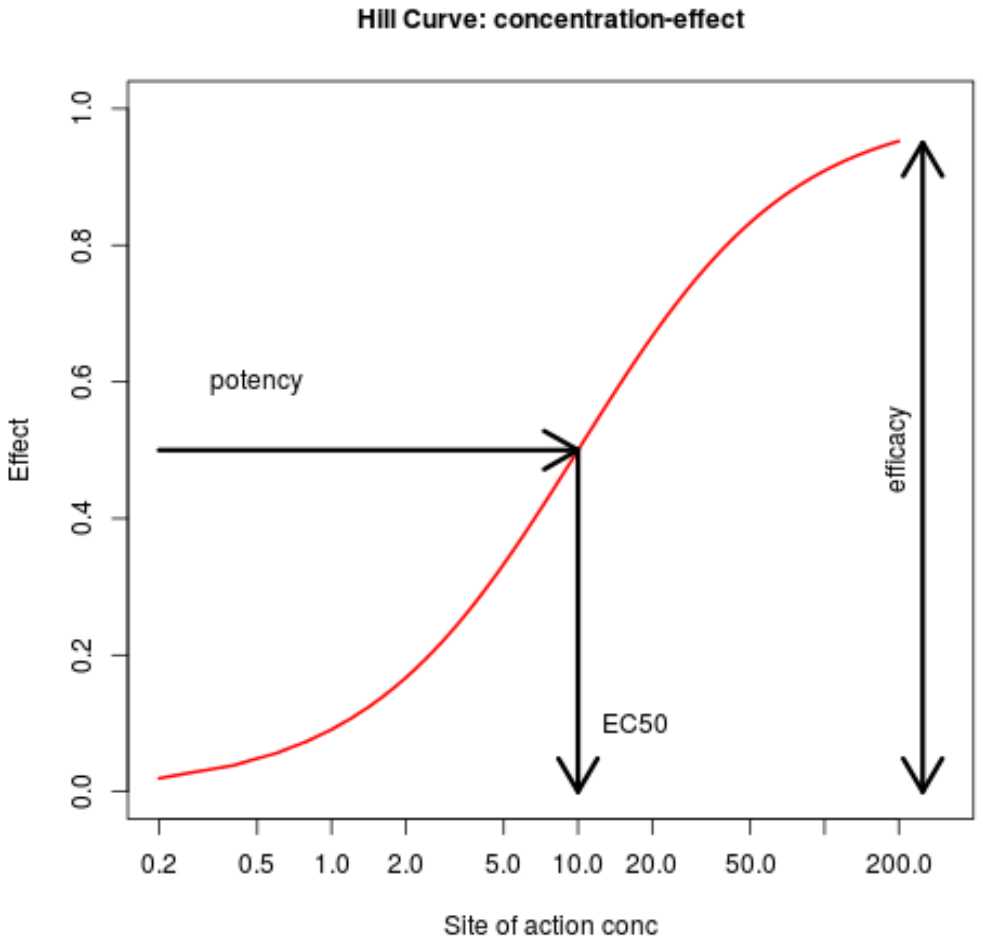
Assume finite receptor capacity

$$[R_{tot}] = [R] + [DR]. \quad (7)$$

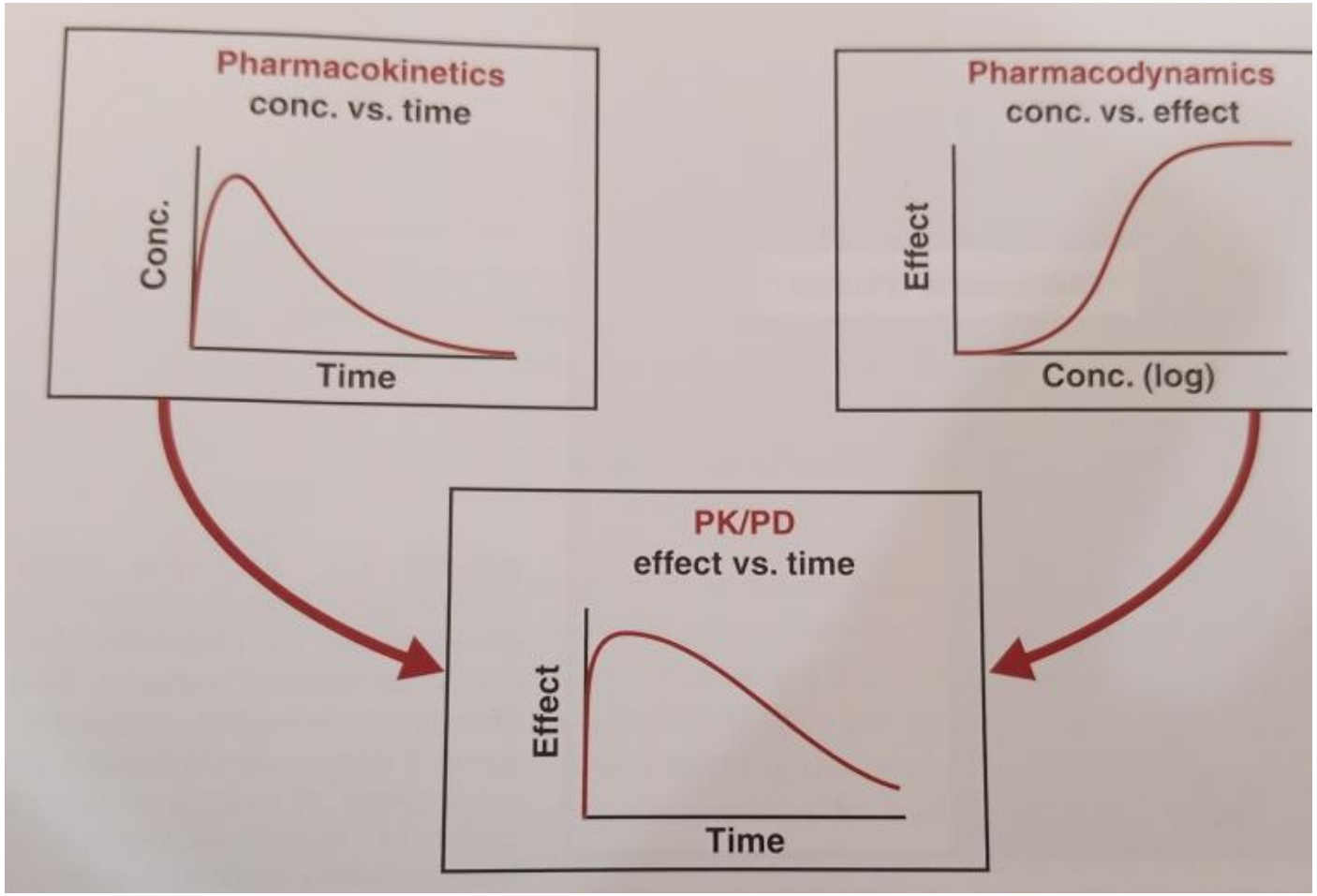
Remove dependence of $[DR]$ on $[R]$, assume

$Effect \propto [DR]$, and can show $EC_{50} = \frac{Koff}{Kon}$

$$Effect = E_{max} \frac{C^{\gamma}}{E_{C50}^{\gamma} + C^{\gamma}}. \quad (8)$$



Rational selection of optimal dosing regimen requires integrating PK/PD



- Video: Getting the dose right

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PKPD modelling

- Modelling PKPD with time usually complicated by not measuring PK at the site of effect
- Often neglected by traditional medical statistical analysis taking single PD measure, but increased power can be leveraged by modelling PD endpoint with time
- Modelling approaches include “effect compartment” and use of “turnover” models
- K-PD models analyse dose-response (no PK), estimate an apparent decay in drug effect with time

Summary

- Models in PKPD can be more useful than descriptive analysis
- Most models are nonlinear
- By choosing models with a biological basis, "prior" information can be incorporated
- PK alone is useful for bioequivalence, studying drug interactions
- PK linked with PD more useful in the clinical setting e.g. for dose recommendation

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thank you | enkosi | dankie