Pharmacometrics

Introduction to Pharmacodynamics

Novartis-Academia Hackathon

Andrew Stein, PhD
Associate Director Pharmacometrics
Cambridge, MA **August 2019**

NOVARTIS

Overview

- Target Audience: people with a quantitative background that are new to pharmacometrics.
  - Simple differential equations will be used
- Topics covered
  - Key mathematical results for pharmacodynamic models
  - Introduction and motivation for the Emax model
  - Introduction to immediate and delayed effect PKPD models

Acknowledgements
(Based on material from)

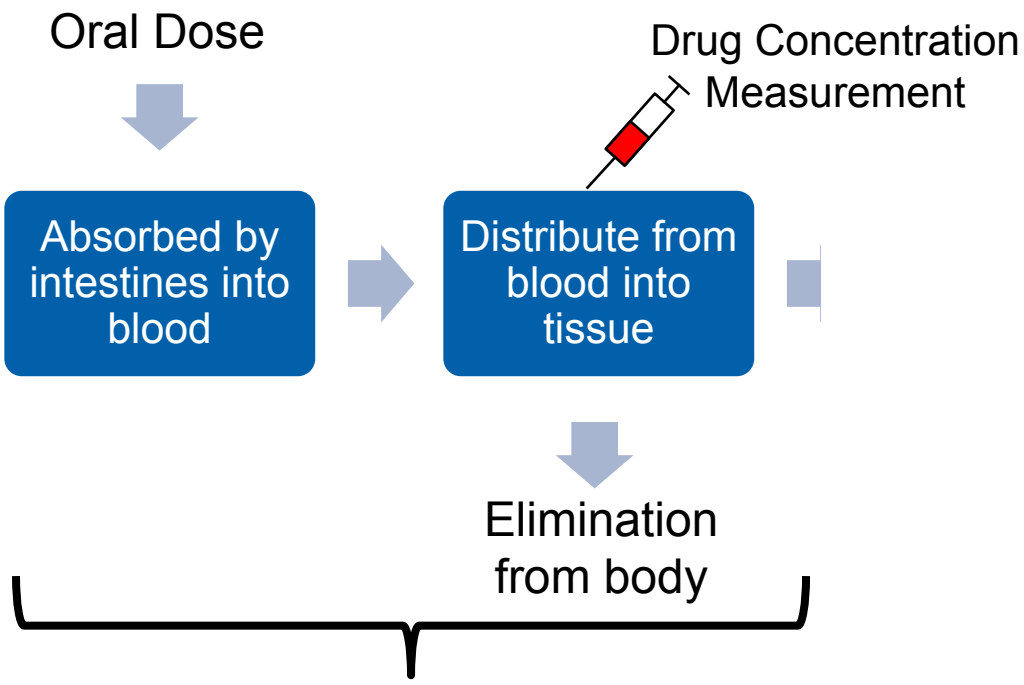
- Rowland, M., Tozer, T. N. *Clinical pharmacokinetics and pharmacodynamics: concepts and applications*
- Peter Bonate, Astellas
- Richard Brundage, U Minnesota
- Leon Aarons, U Manchester
- Jean-Louis Steimer, Novartis
- Martin Fink, Novartis
- Nick Holford, U Auckland http://holford.fmhs.auckland.ac.nz/Teaching/pharmacometrics/advanced.php

Pharmacodynamics

What the drug does to the body

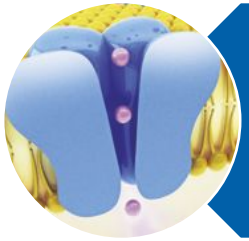
NOVARTIS

The “PKPD” pathway of drug effect



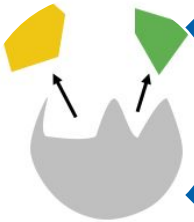
Should children and adults receive the same dose?

Main targets for drugs

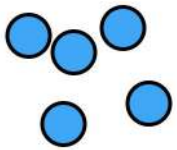


Receptors

- Signal Transduction
- Ion Channels



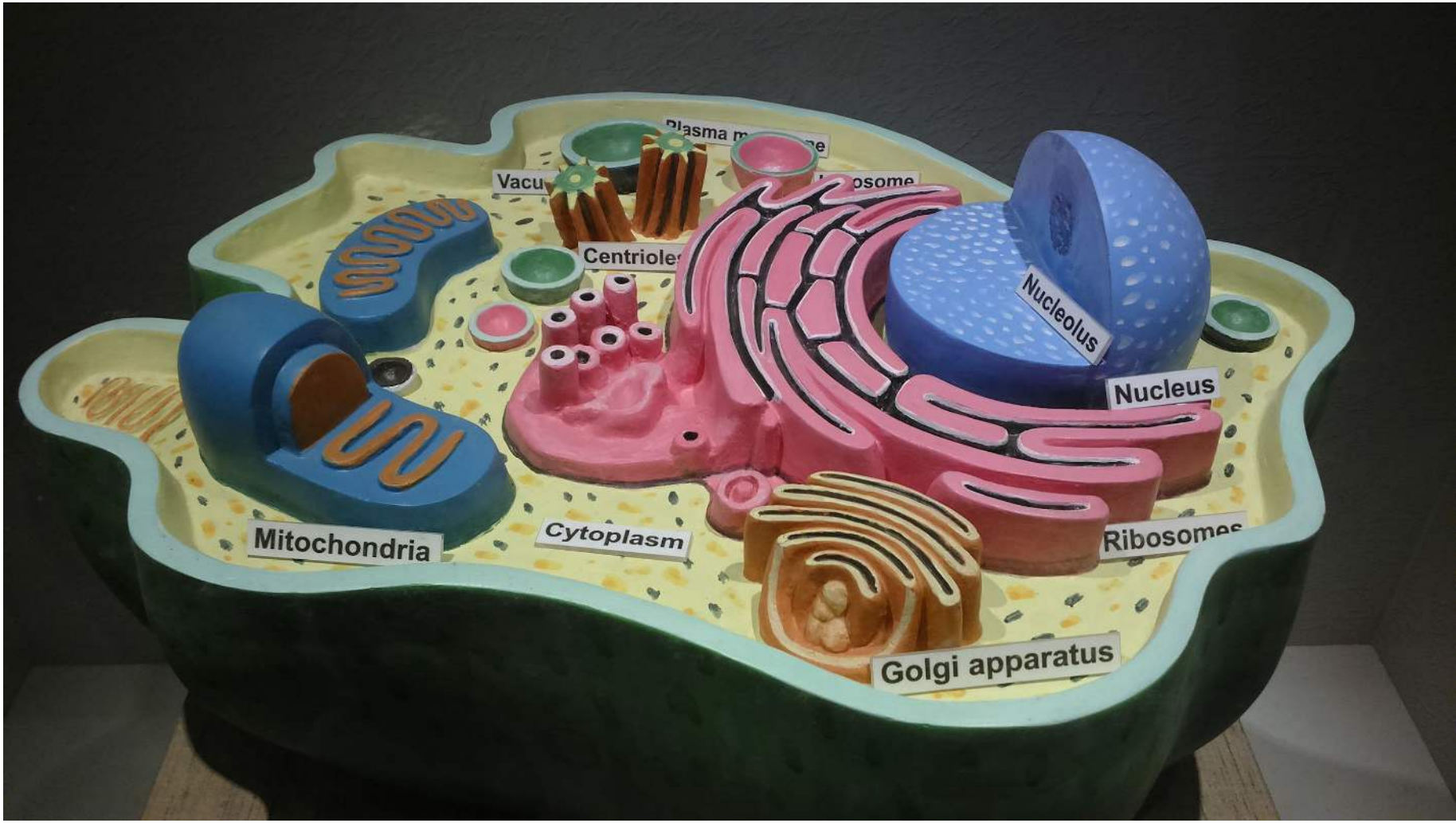
Enzymes



Soluble agents

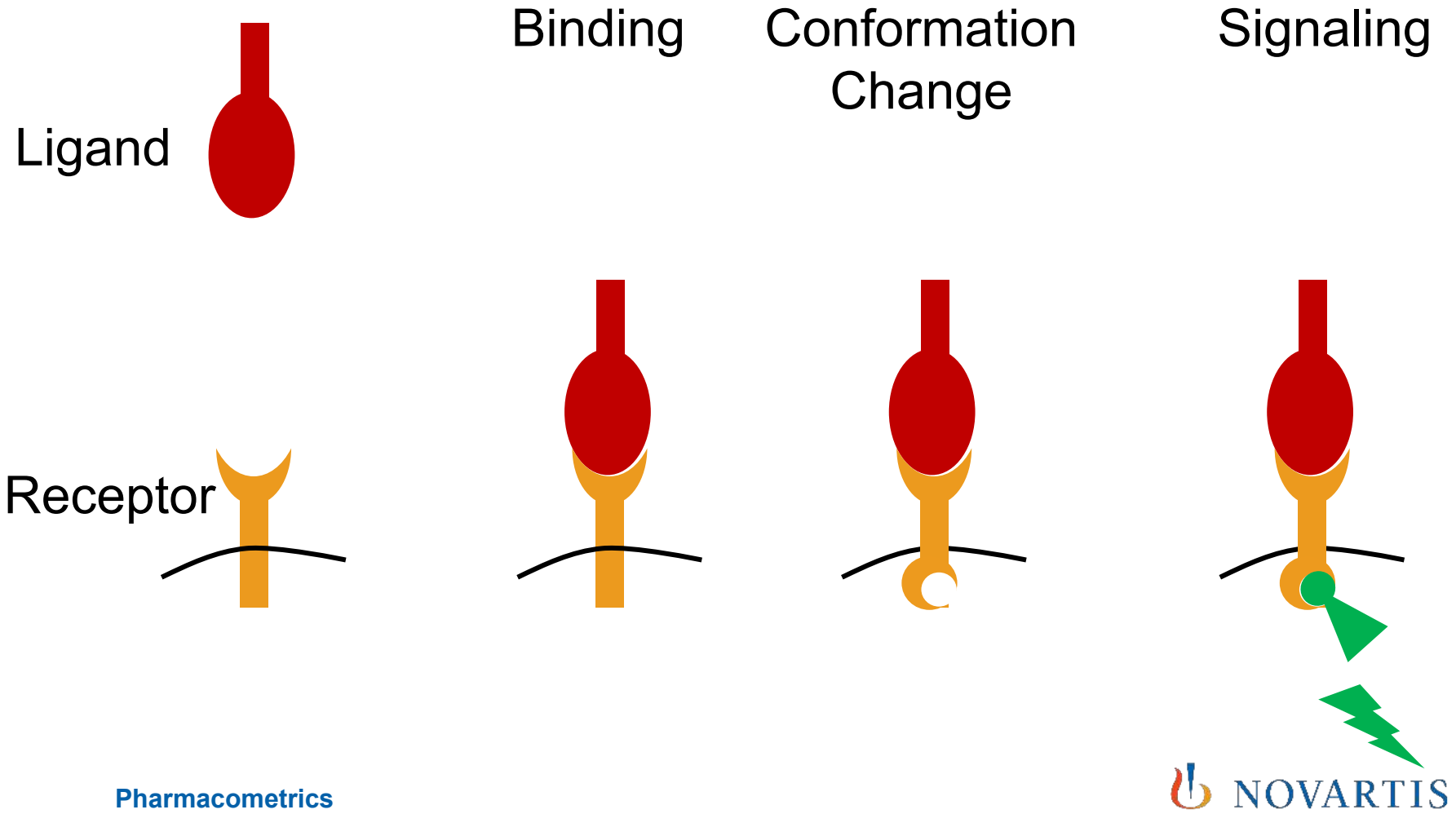
- Cytokines

Cell

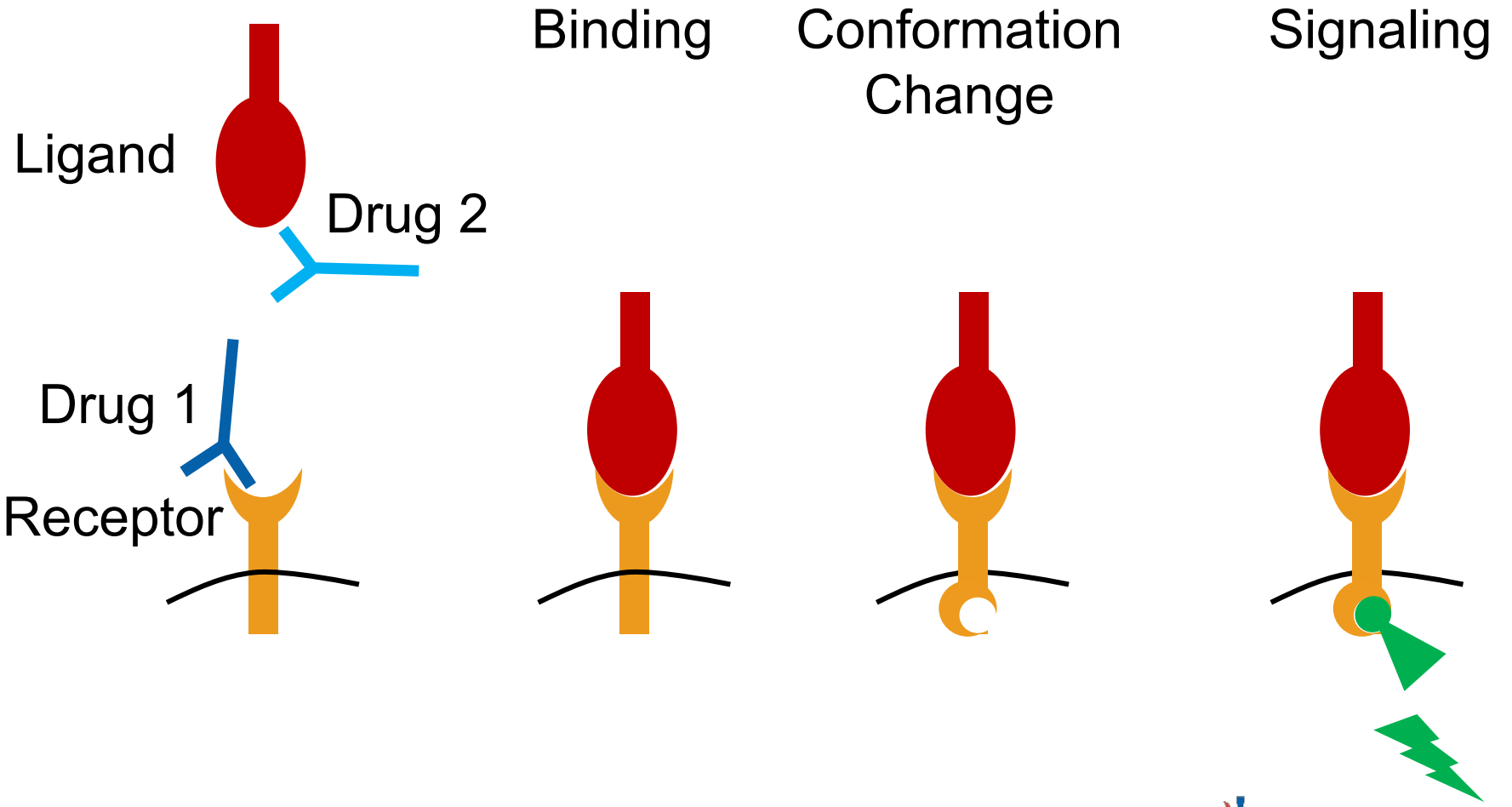


wikipedia

Receptor – Signal Transduction

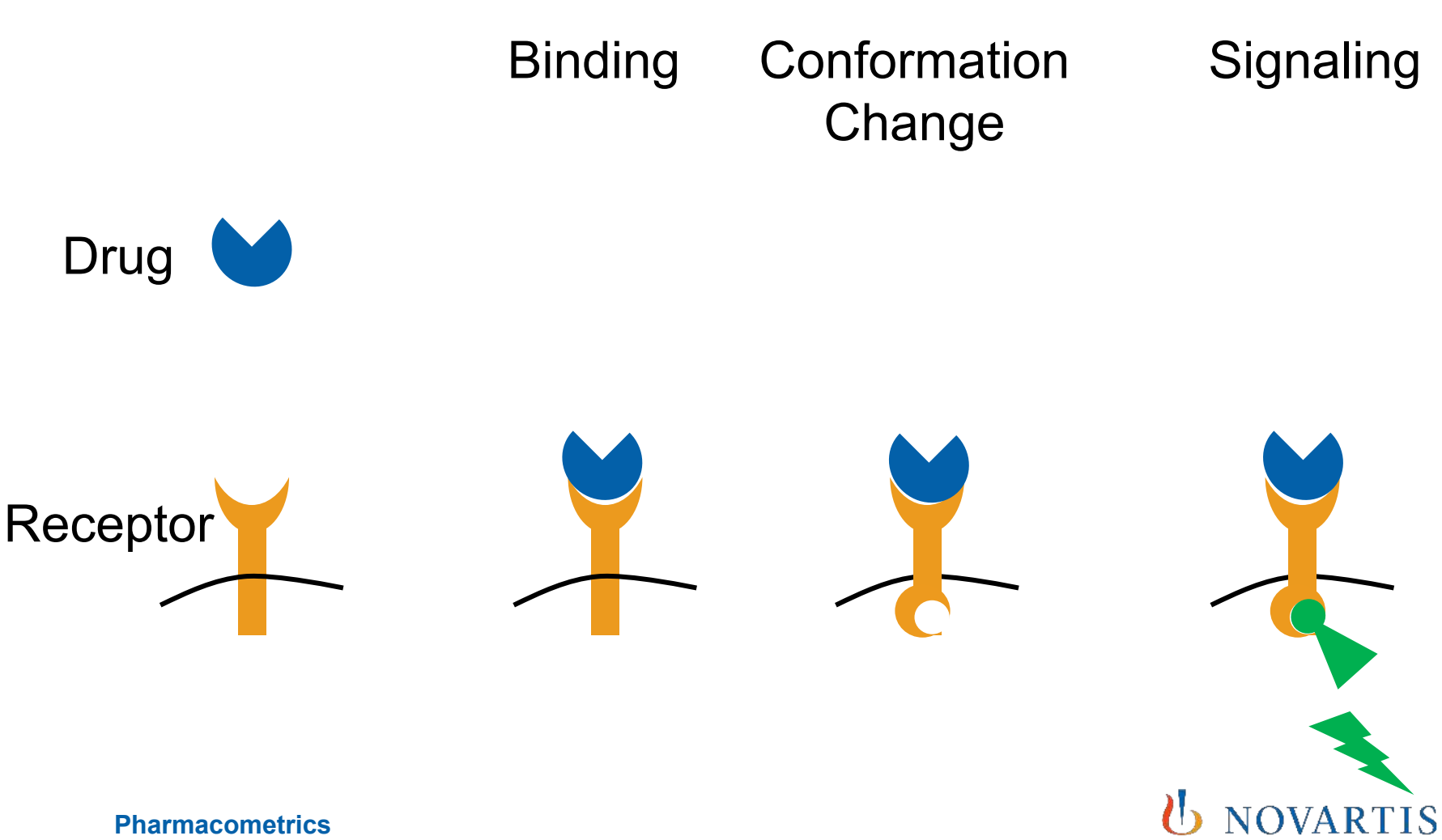


Drug can block binding and inhibit signaling (antagonist)

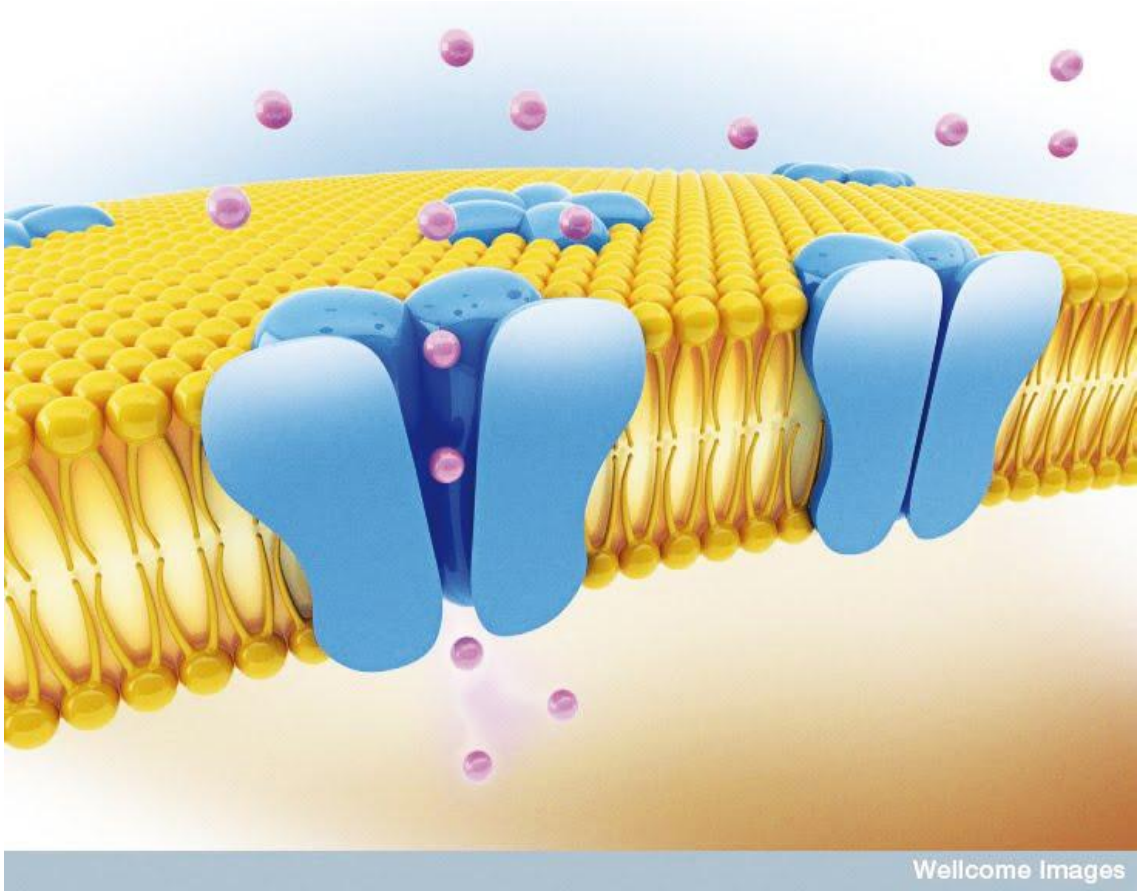


NOVARTIS

Drug can enhance signaling (agonist)



Receptor - Ion channel

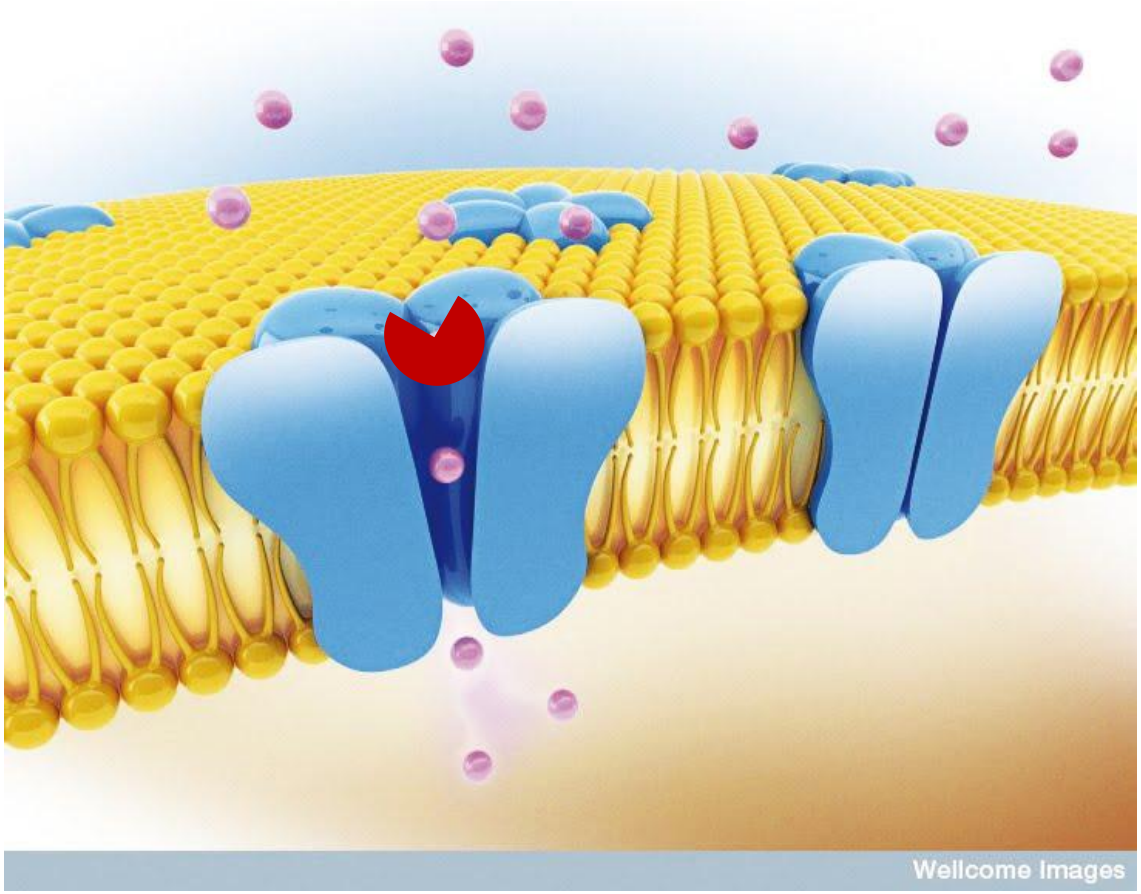


Cell membrane receptors allow the outside of the cell to communicate with the inside of the cell

NOVARTIS

From Peter Bonate

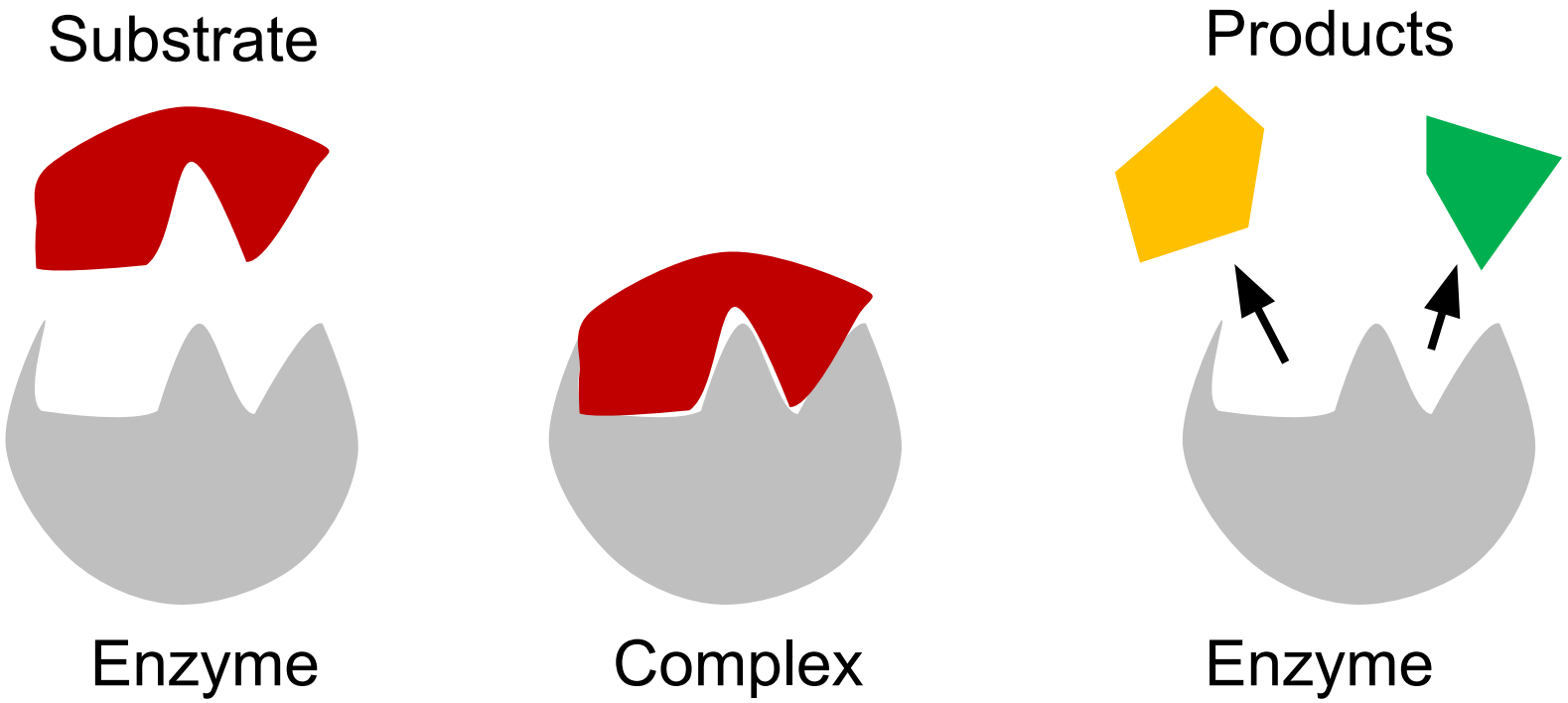
Drug can keep an ion channel open or closed



NOVARTIS

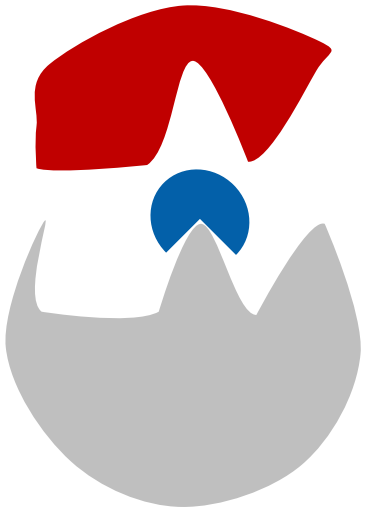
From Peter Bonate

Enzyme kinetics



Drug interference with enzyme

Substrate



Enzyme

Classical Binding Theory

$$\frac{d(CR)}{dt} = k_{on}C \cdot R - k_{off}(CR)$$

The dissociation constant gives the equilibrium drug concentration

$$0 = \frac{d(CR)}{dt} = k_{on} C \cdot R - k_{off}(CR)$$

$$k_{on} C \cdot R = k_{off}(CR)$$

$$\frac{C \cdot R}{(CR)} = \boxed{\frac{k_{off}}{k_{on}} = K_d}$$ dissociation constant

The dissociation constant tells you how tightly the drug binds

We want a formula for what fraction of the target is free.

Total drug: $C_{tot} = C + (CR)$

Total target: $R_{tot} = R + (CR)$

Dissociation Constant: $(C)(R) = \mathrm{K_d}(CR)$

Given a starting drug concentration, what is percent of free target: R/R_{tot}?

Solving for free target

Total drug: $C_{tot} = C + (CR)$

Total target: $R_{tot} = R + (CR)$

Dissociation Constant: $(C)(R) = K_d(CR)$

$$(C)(R) = K_d(R_{tot} - R)$$

$$(C)(R) = K_d R_{tot} - K_d R$$

$$(C + K_d)(R) = K_d R_{tot}$$

$$\frac{R}{R_{tot}} = \frac{K_d}{C + K_d}$$

Solving for target occupancy

$$\frac{R}{R_{tot}} \approx \frac{K_d}{C + K_d}$$

Total target: $R_{tot} = R + (CR)$

$$\frac{R_{tot}}{R_{tot}} = \frac{R}{R_{tot}} + \frac{CR}{R_{tot}} = 1$$

$$\frac{CR}{R_{tot}} = 1 - \frac{R}{R_{tot}}$$

$$\frac{CR}{R_{tot}} = 1 - \frac{K_d}{C + K_d}$$

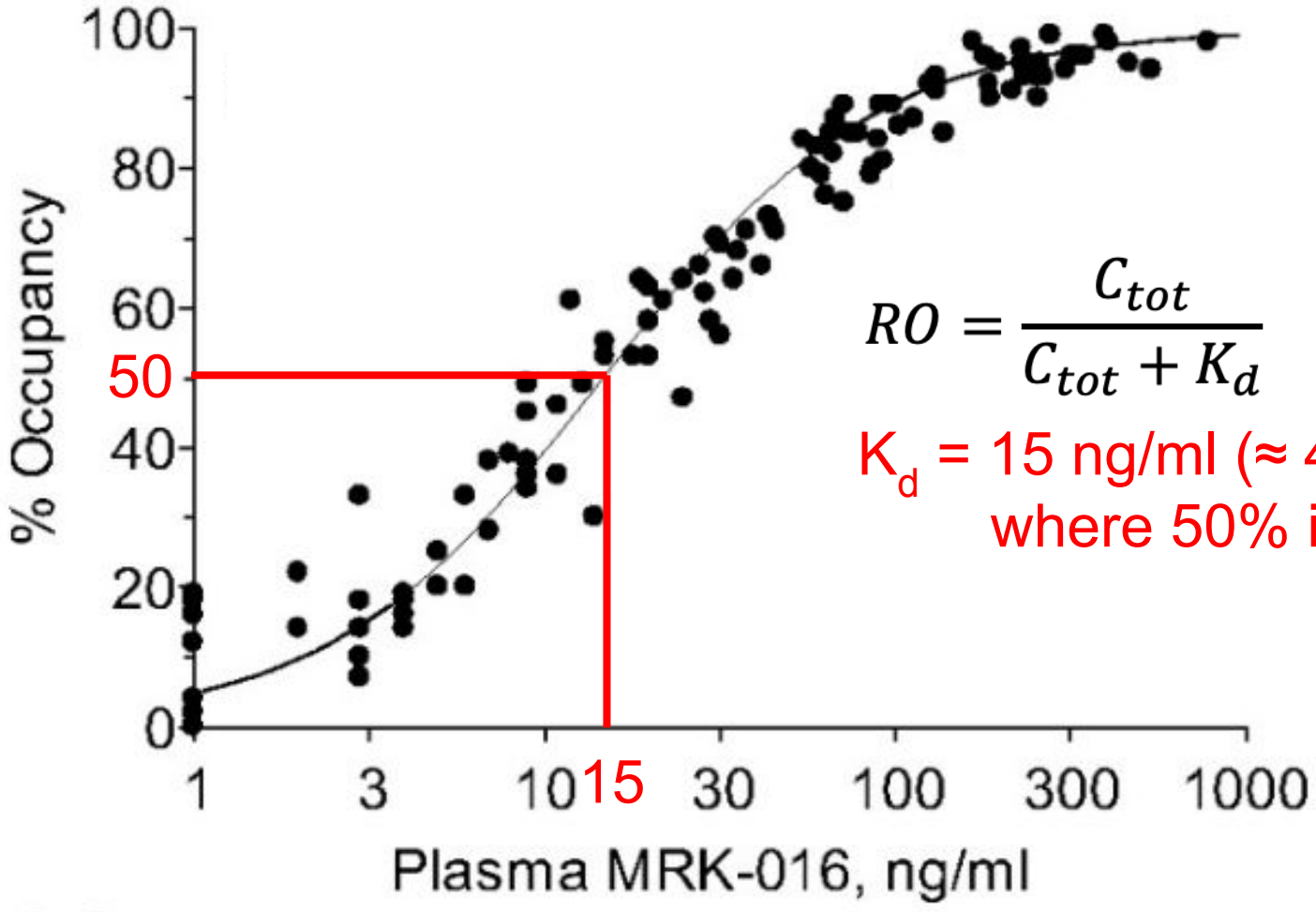
$$\frac{CR}{R_{tot}} = \frac{C}{C + K_d}$$

If target is a receptor, this is called receptor occupancy (RO)

$$RO = \frac{CR}{R_{tot}} \approx \frac{C_{tot}}{C_{tot} + K_d}$$

When $R_{tot} >> K_d$

Receptor occupancy data

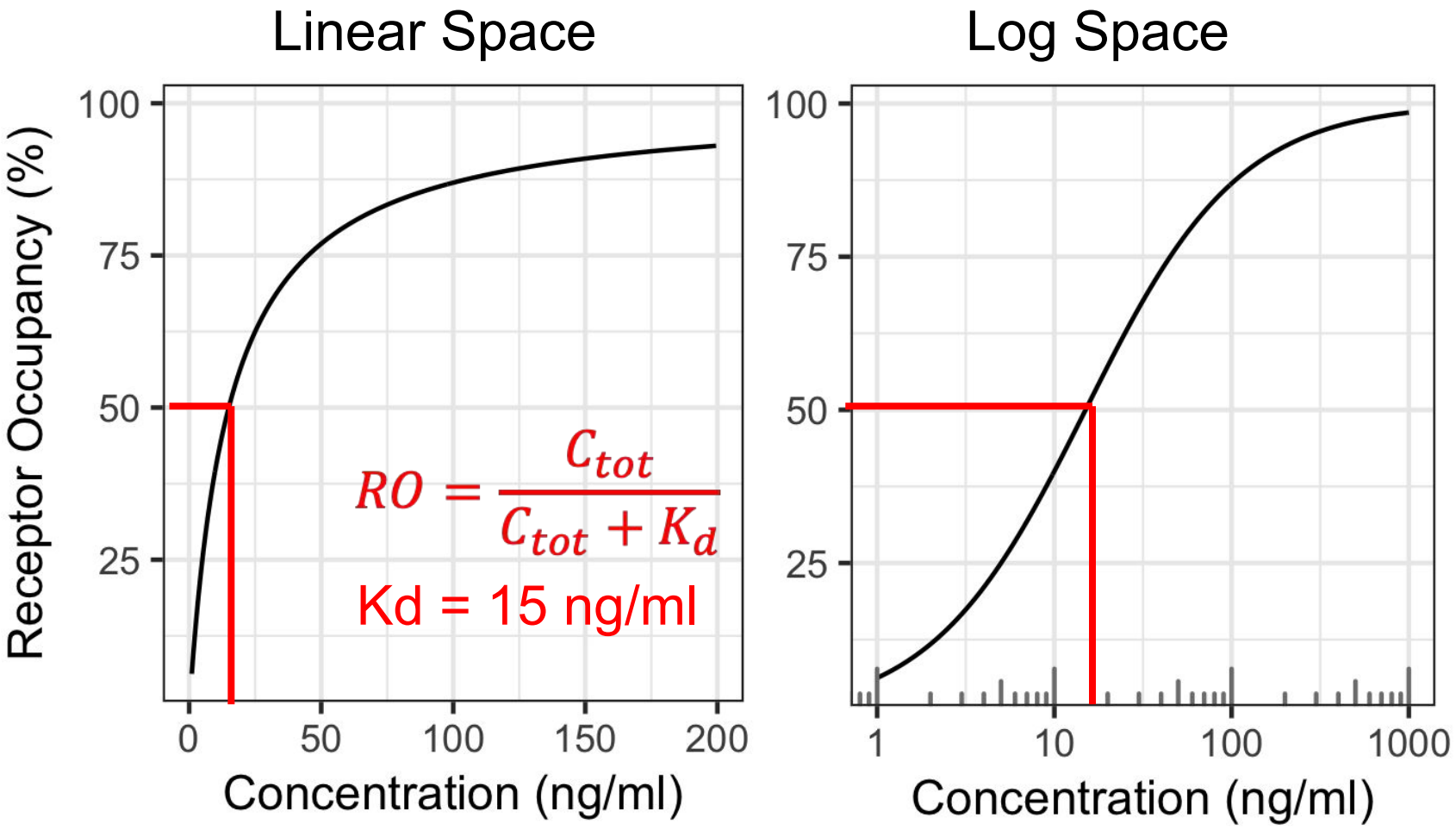


$$RO = \frac{C_{tot}}{C_{tot} + K_d}$$

K_d = 15 ng/ml (≈ 40 nM)
where 50% is bound

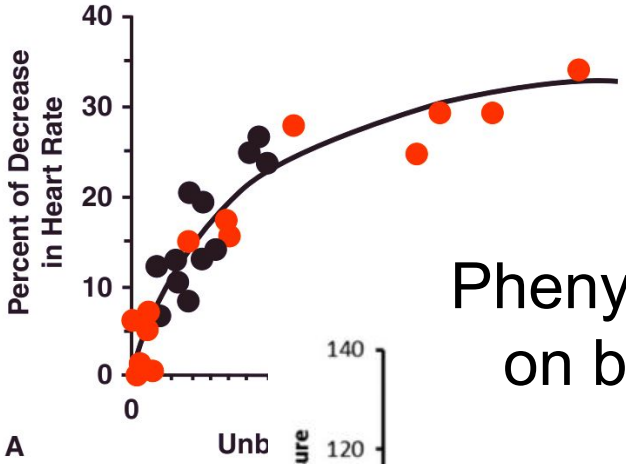
Atack, John R., et al. "In vitro and in vivo properties of 3-tert-butyl-7-(5-methylisoxazol-3-yl)-2-(1-methyl-1H-1, 2, 4-triazol-5-ylmethoxy)-pyrazolo [1, 5-d]-[1, 2, 4] triazine (MRK-016), a GABAA receptor α5 subtype-selective inverse agonist." Journal of Pharmacology and Experimental Therapeutics 331.2 (2009): 470-484.

Receptor occupancy in linear and log space



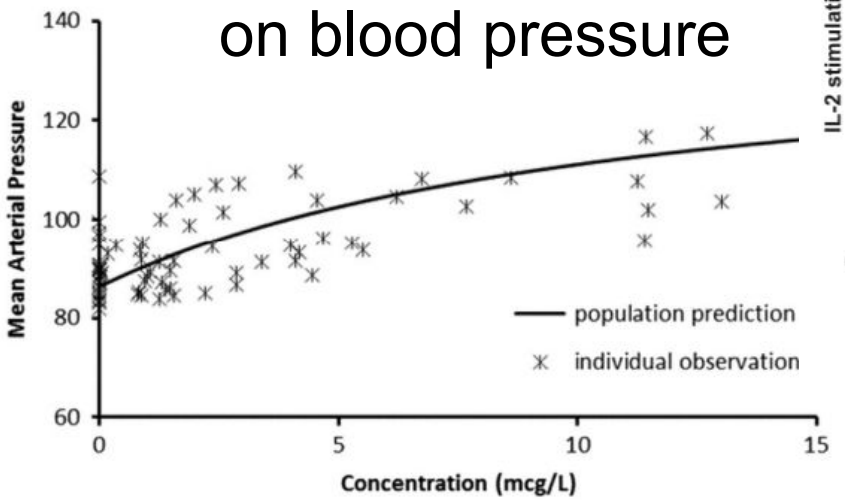
Receptor occupancy type curves describes a lot of data

Propafol effect on heart rate



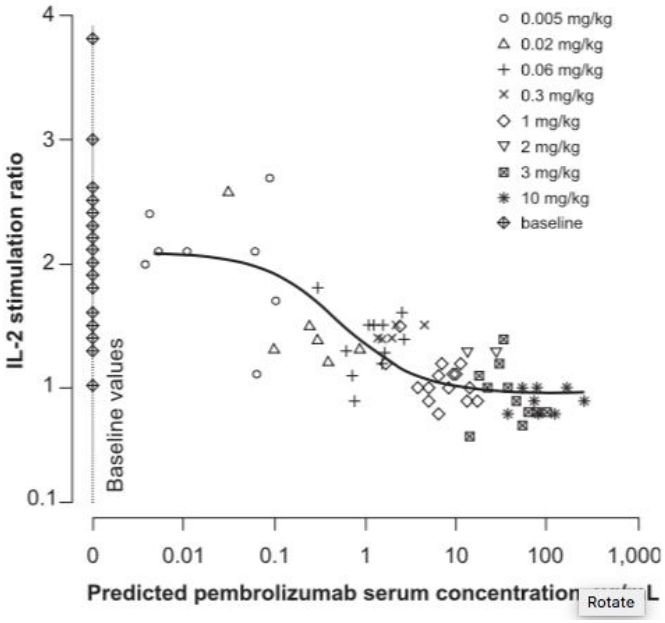
Rowla

Phenylepherine effect on blood pressure



Atkinson, Hartley C., Amanda L. Potts, and Brian J. Anderson. "Potential cardiovascular adverse events when phenylephrine is combined with paracetamol: simulation and narrative review." *European journal of clinical pharmacology* 71.8 (2015): 931-938.

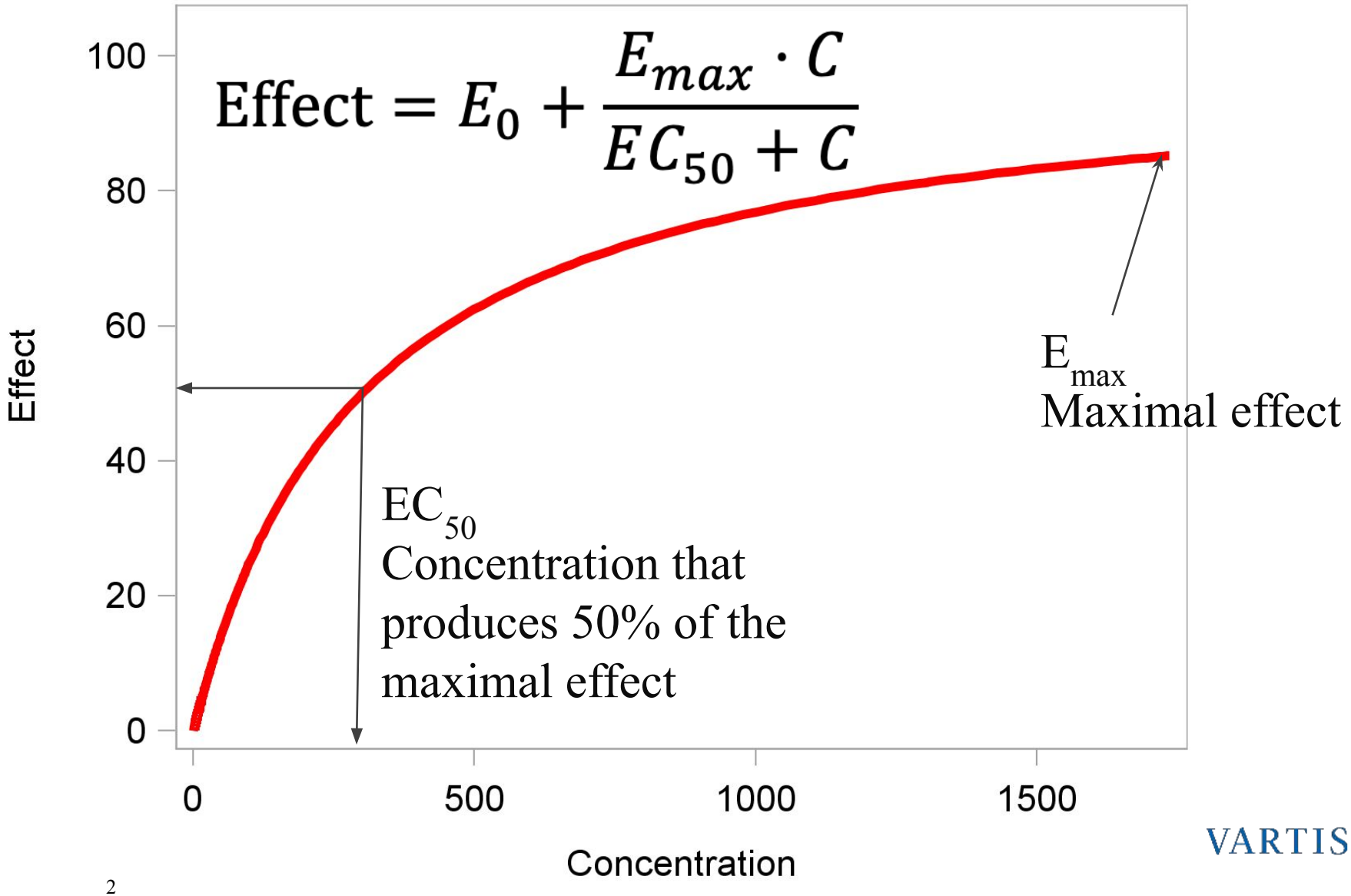
Keytruda effect on IL-2 stimulation



Elassaiss-Schaap, J., et al. "Using model-based "learn and confirm" to reveal the pharmacokinetics-pharmacodynamics relationship of pembrolizumab in the KEYNOTE-001 Trial." CPT: pharmacometrics & systems pharmacology 6.1 (2017): 21-28.

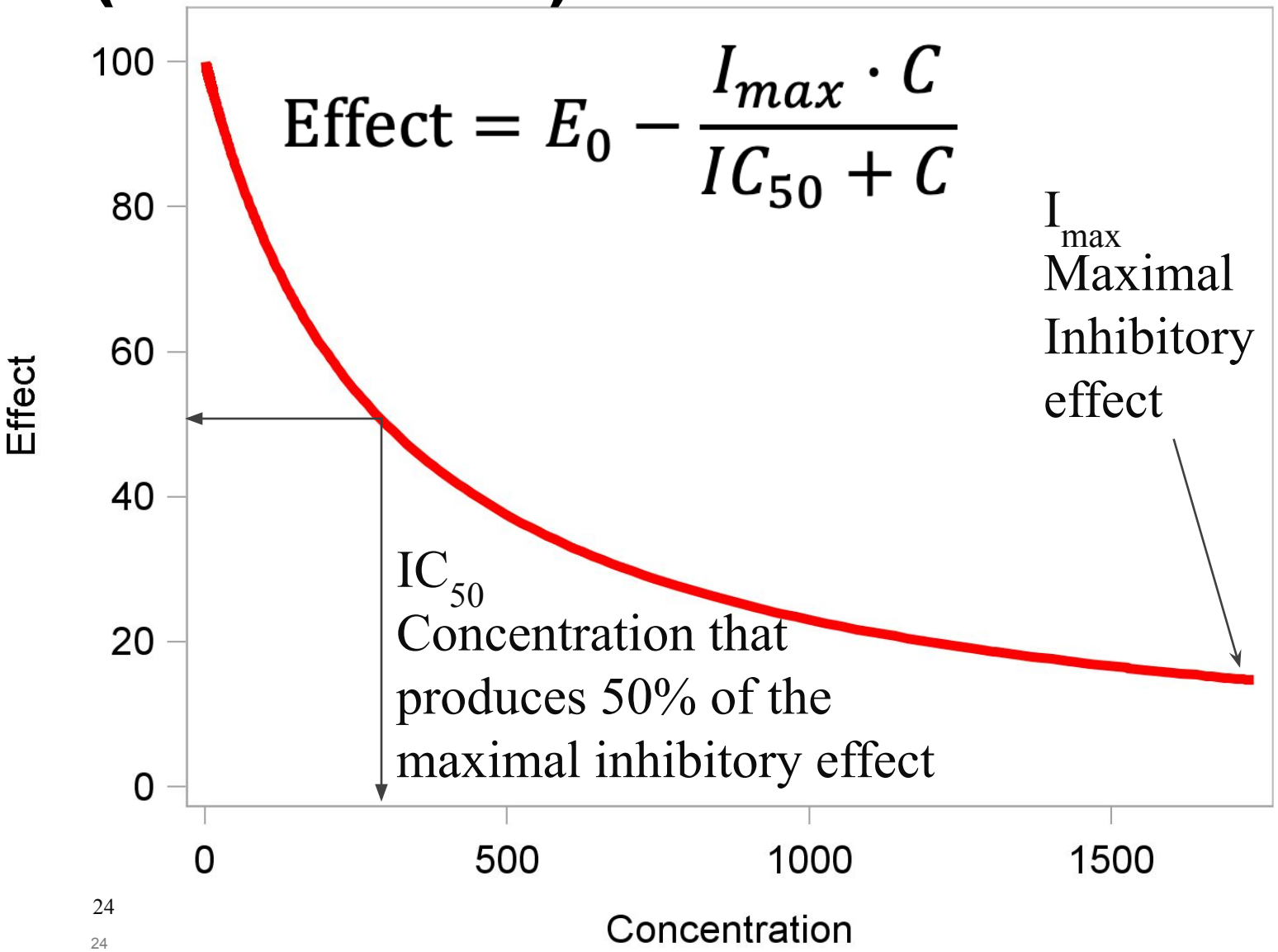
NOVARTIS

Emax model – positive effect



VARTIS

Imax model – negative effect (I = inhibition)

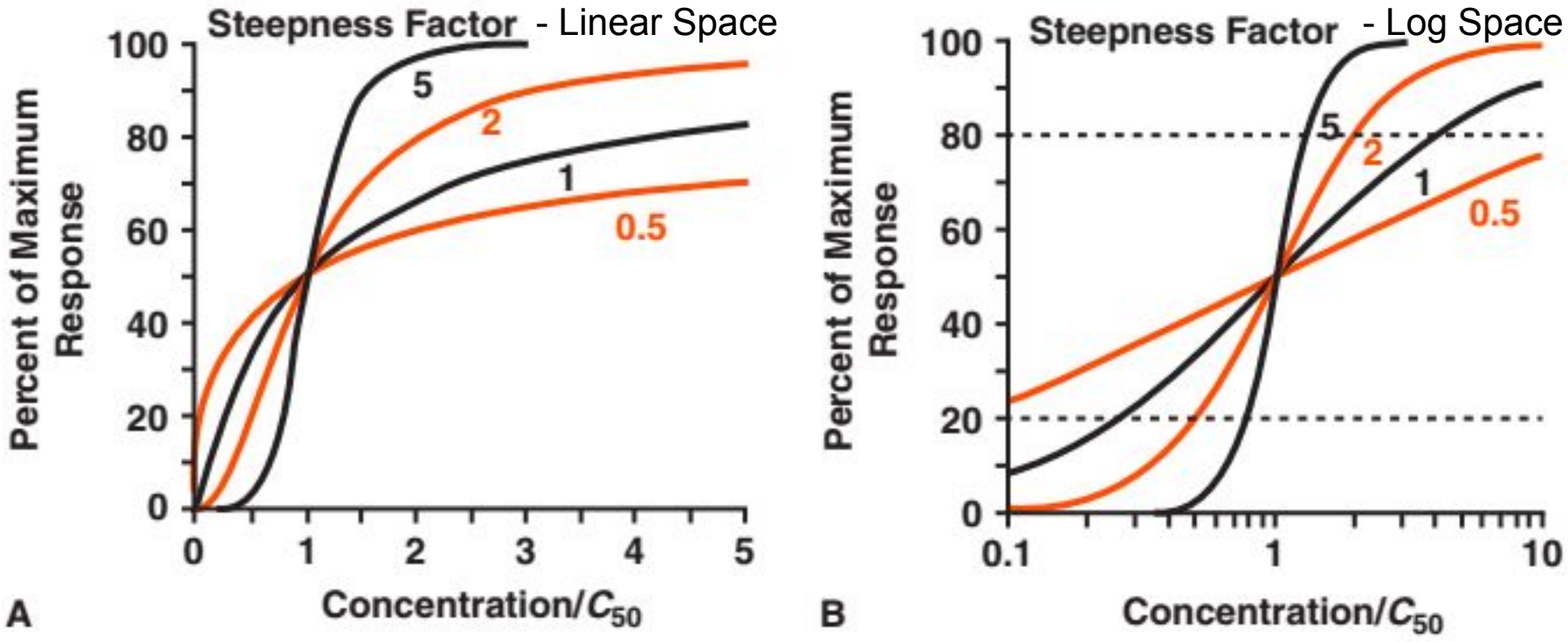


24

VARTIS

Adding in a steepness factor

$$\text{Effect} = \frac{C^{\gamma}}{C^{\gamma} + EC_{50}^{\gamma}}$$



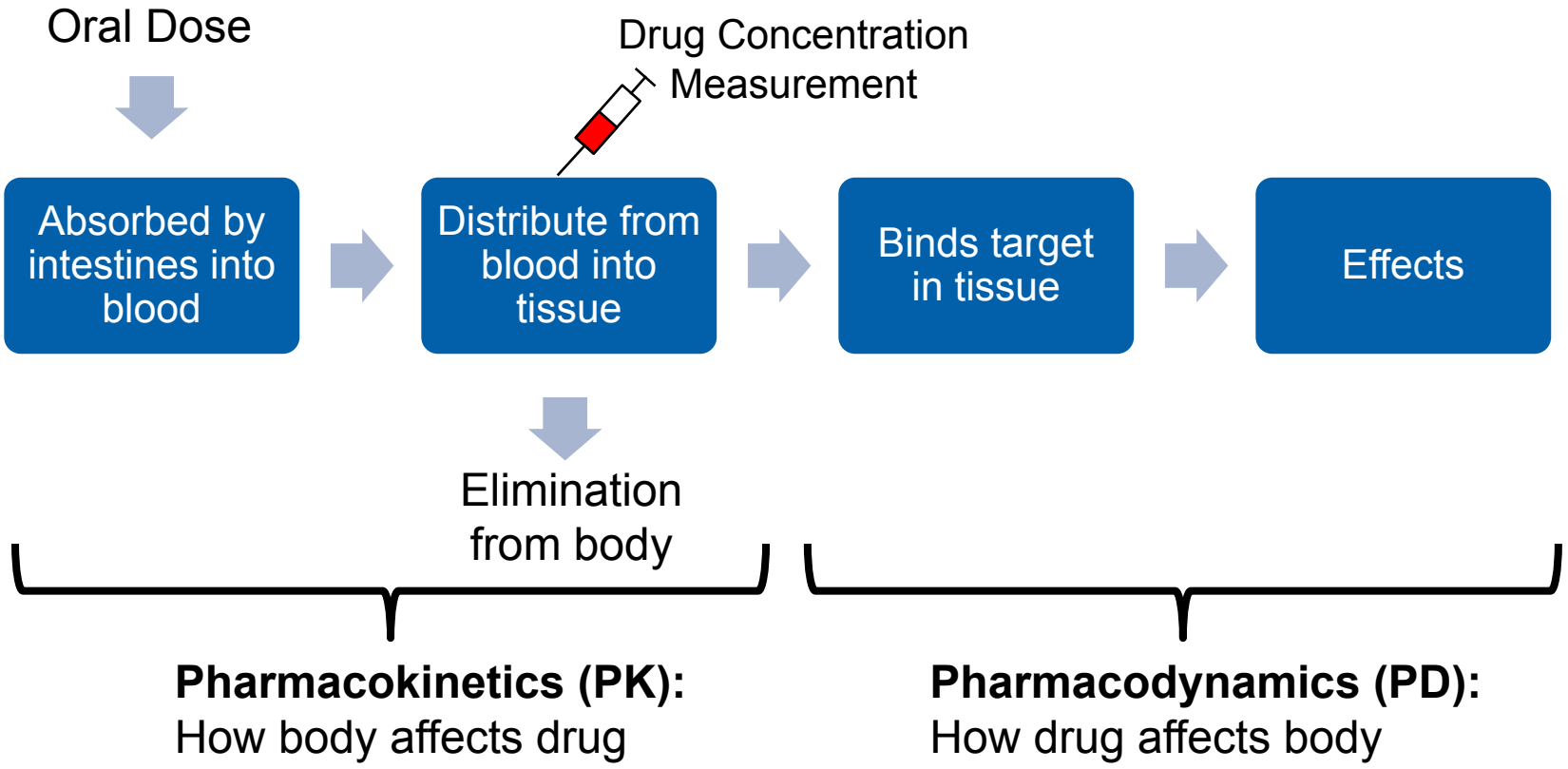
Rowland and Tozer

Pharmacokinetics and Pharmacodynamics

Putting it all together

NOVARTIS

The “PKPD” pathway of drug effect

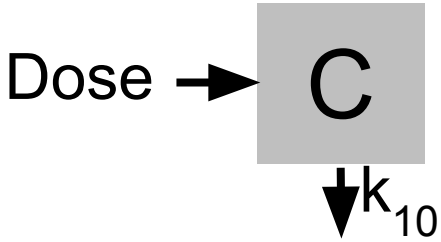


NOVARTIS

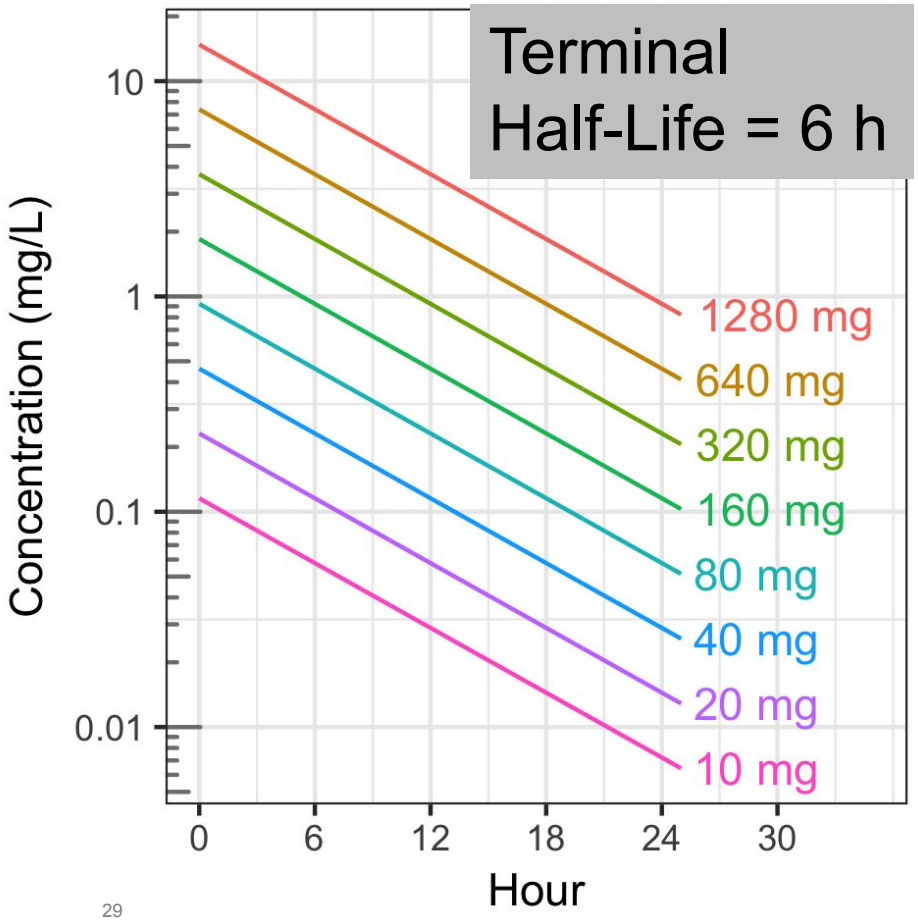
Overview – Drug effect/response

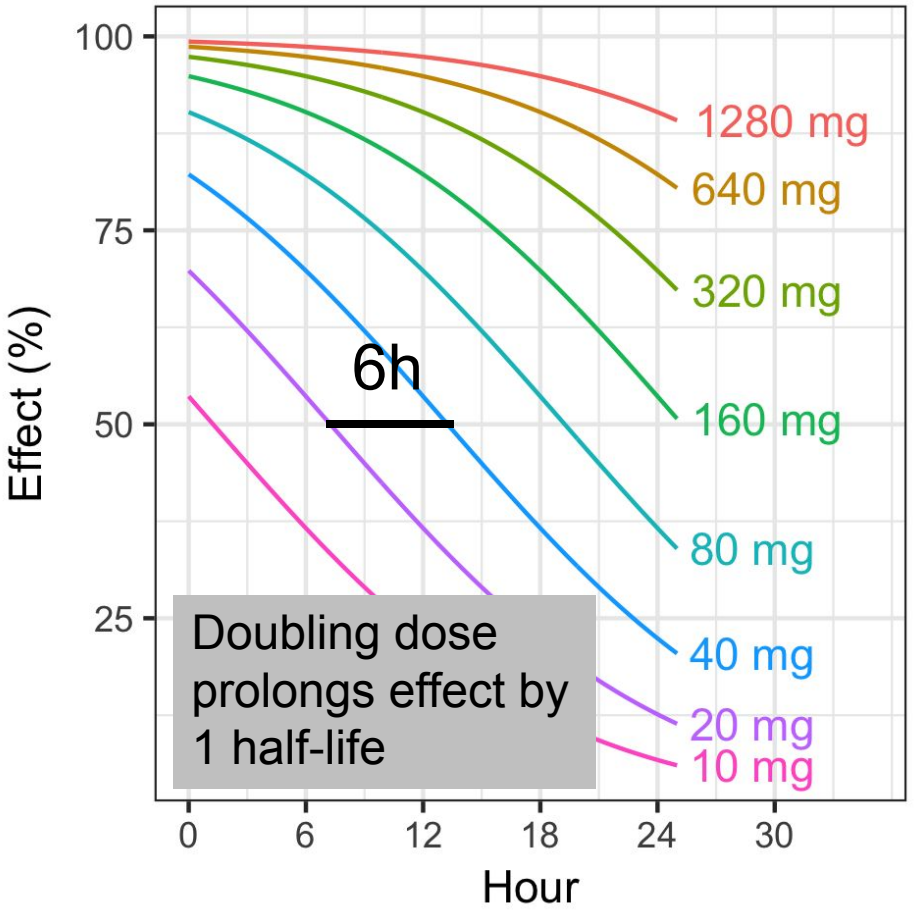
- Immediate
- Delayed
  - Distributional
- Cumulative
  - Tumor shrinkage
  - Bone remodeling

Immediate Effect



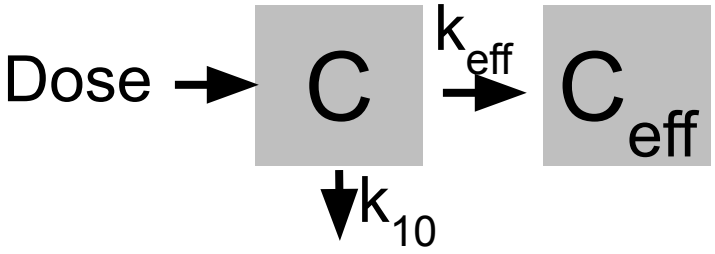
$$\text{Eff} = \frac{E_{max} \cdot C}{EC_{50} + C}$$





Delayed Effect (distributional)

- Measuring drug concentration in tissue is difficult
- But it takes time for drug to distribute to tissue



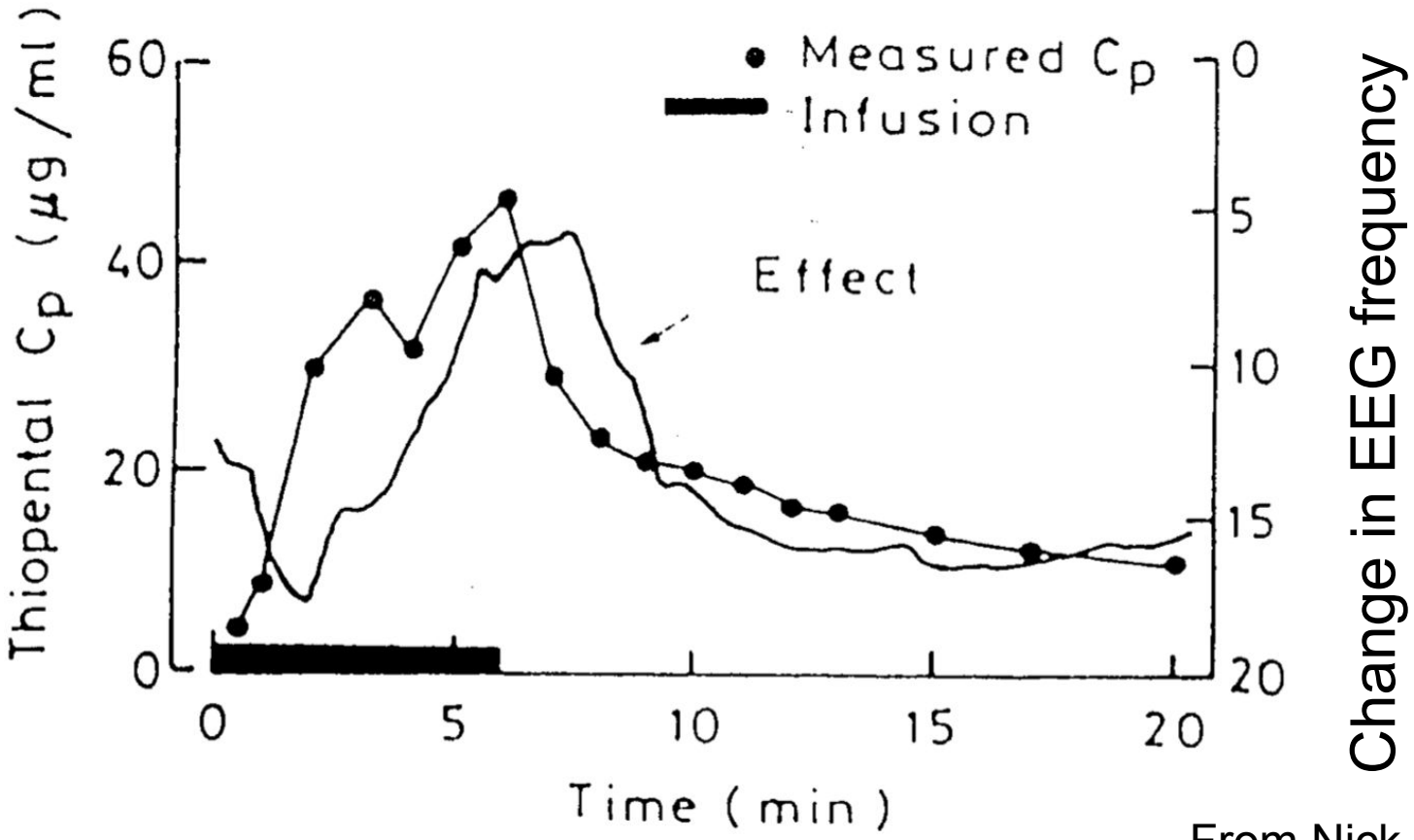
$$\text{Eff} = \frac{E_{max} \cdot C_{\text{eff}}}{EC_{50} + C_{\text{eff}}}$$

$$\frac{dC}{dt} = -k_{10} \cdot C$$

$$\frac{dC_{\text{eff}}}{dt} = -k_{\text{eff}} \cdot (C_{\text{eff}} - C)$$

Effect compartment is “empirical”
We don’t track the mass of drug moving from central to effect compartment

Thiopentone Time Course (anaesthesia drug)

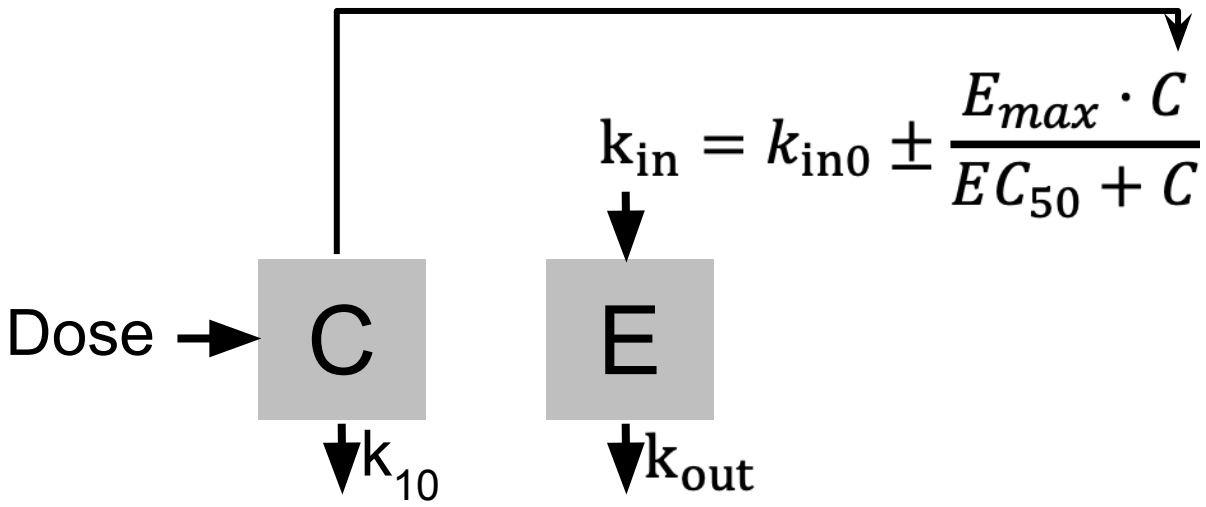


From Nick Holford

Stanski DR, Maitre PO. Population pharmacokinetics and pharmacodynamics of thiopental: the effect of age revisited. Anesthesiology. 1990; 72(3):412-22.

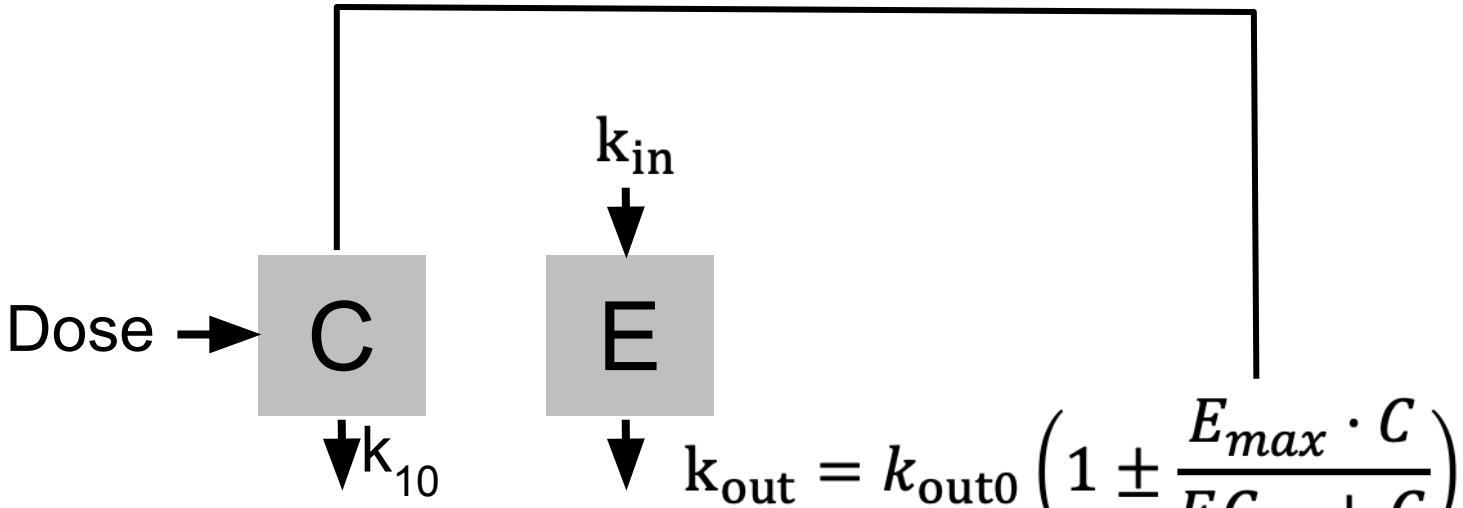
Cumulative Effect (Indirect Response)

- Drug impacts the “rate of change” of the effect
  - Synthesis or degradation of a protein
  - Growing/shrinking tumor
- Could be a stimulatory or inhibitory effect

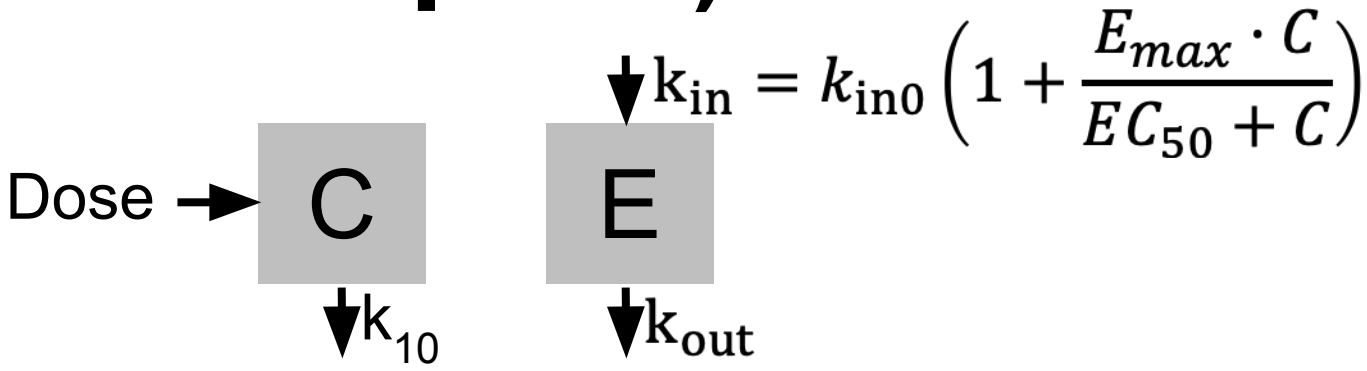


Cumulative Effect (Indirect Response)

- Drug impacts the “rate of change” of the effect
  - Synthesis or degradation of a protein
  - Growing/shrinking tumor
- Could be a stimulatory or inhibitory effect on either the input or the output rate



Cumulative Effect Equations (Indirect Response)



$$\frac{dC}{dt} = -k_{10} \cdot C$$

$$\frac{dE}{dt} = k_{in0}\left(1 + \frac{E_{max} \cdot C}{EC_{50} + C}\right) - k_{out}\, E$$

Effect steady states for indircet response equation

$$\frac{dE}{dt} = k_{in0}\left(1 + \frac{E_{max} \cdot C}{EC_{50} + C}\right) - k_{out}\,E$$

When C=0

At large concentrations,

$$\frac{dE}{dt} = k_{in0} - k_{out}\,E = 0$$

$$E_0 = \frac{k_{in0}}{k_{out}}$$

$$\frac{dE}{dt} = k_{in0}(1 + E_{max}) - k_{out}\,E = 0$$

$$E_{ss,max} = \frac{k_{in0}(1 + E_{max})}{k_{out}}$$

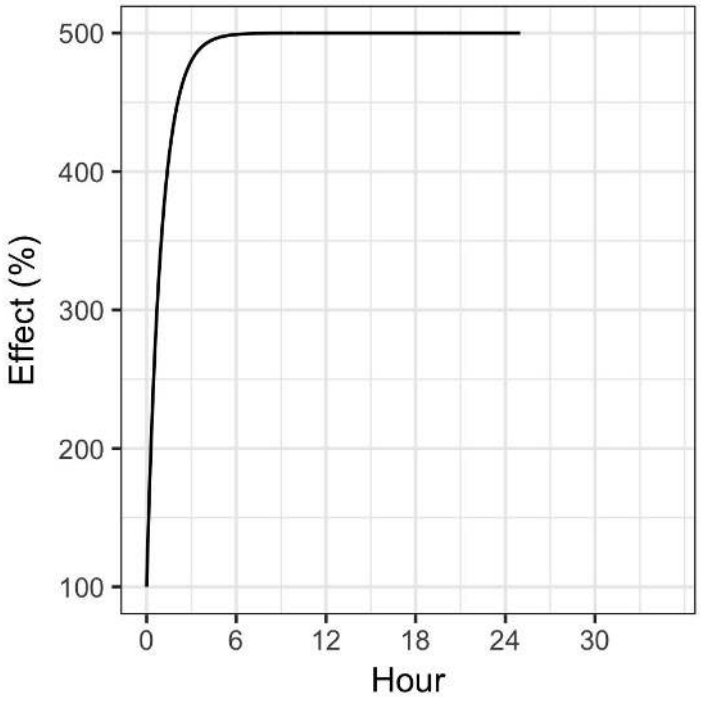
Solution for very large concentration

$$\frac{dE}{dt} \approx k_{in0}(1 + E_{max}) - k_{out}\,E$$

$$E_0 = \frac{k_{in0}}{k_{out}}$$

$$E_{ss,max} = \frac{k_{in0}(1 + E_{max})}{k_{out}}$$

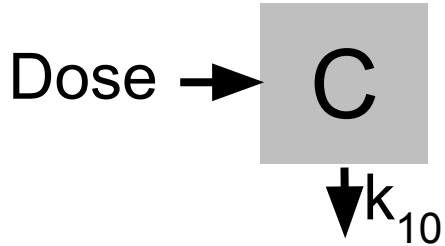
$$E(t) = E_{ss,max} + \left(E_0 - E_{ss,max}\right)e^{-k_{out}t}$$

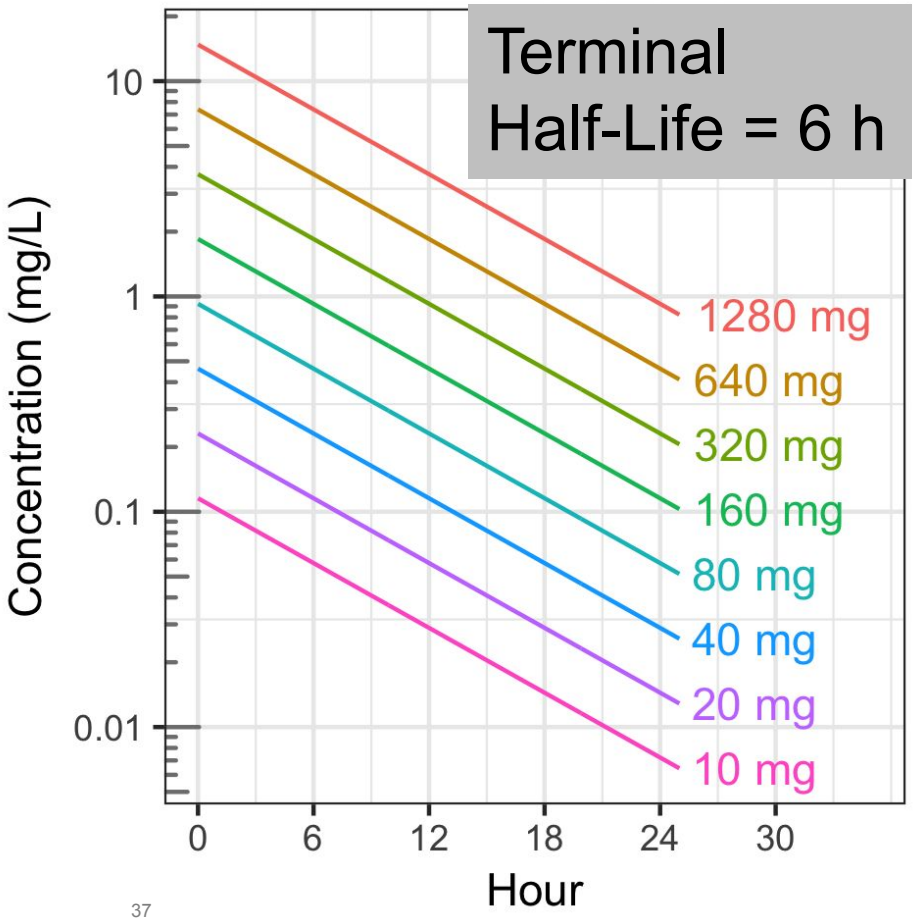


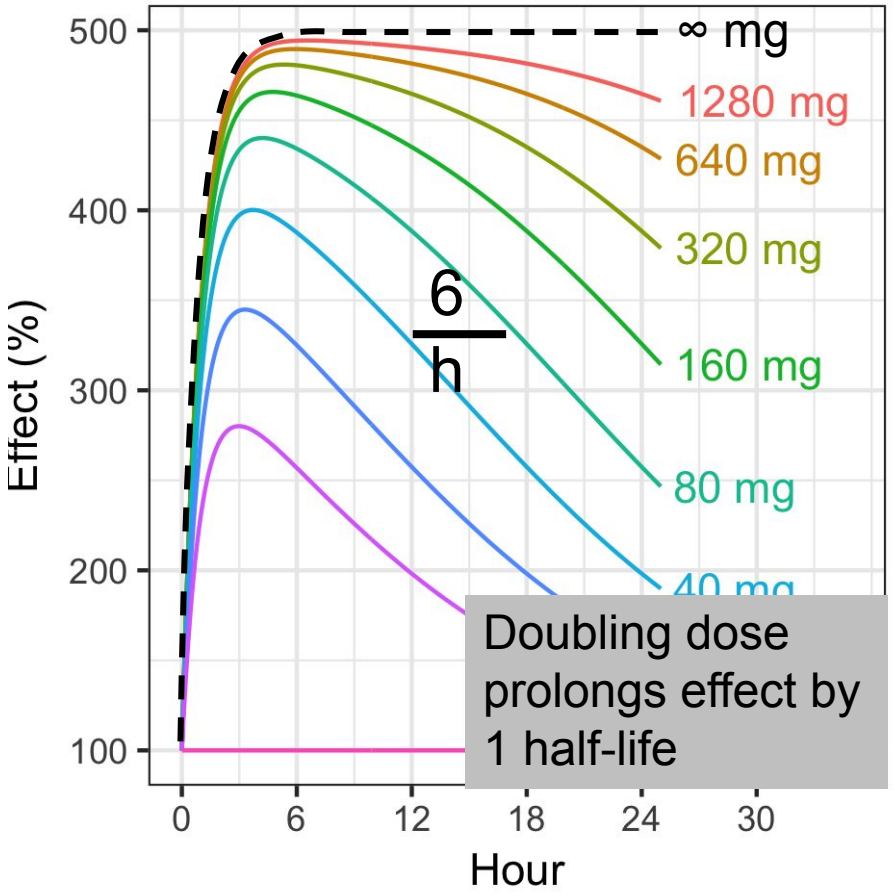
NOVARTIS

Cumulative Effect

$$k_{in} = k_{in0}\left(1 + \frac{E_{max} \cdot C}{EC_{50} + C}\right)$$

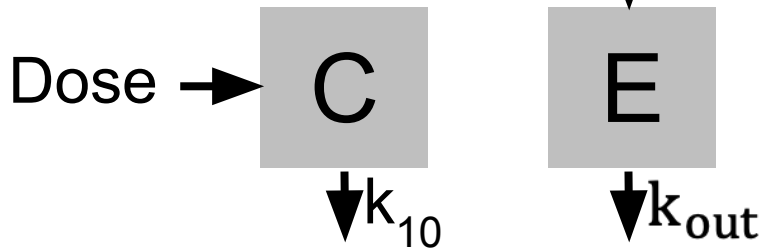






Cumulative Effect

$$k_{in} = k_{in0}\left(1 + \frac{E_{max} \cdot C}{EC_{50} + C}\right)$$

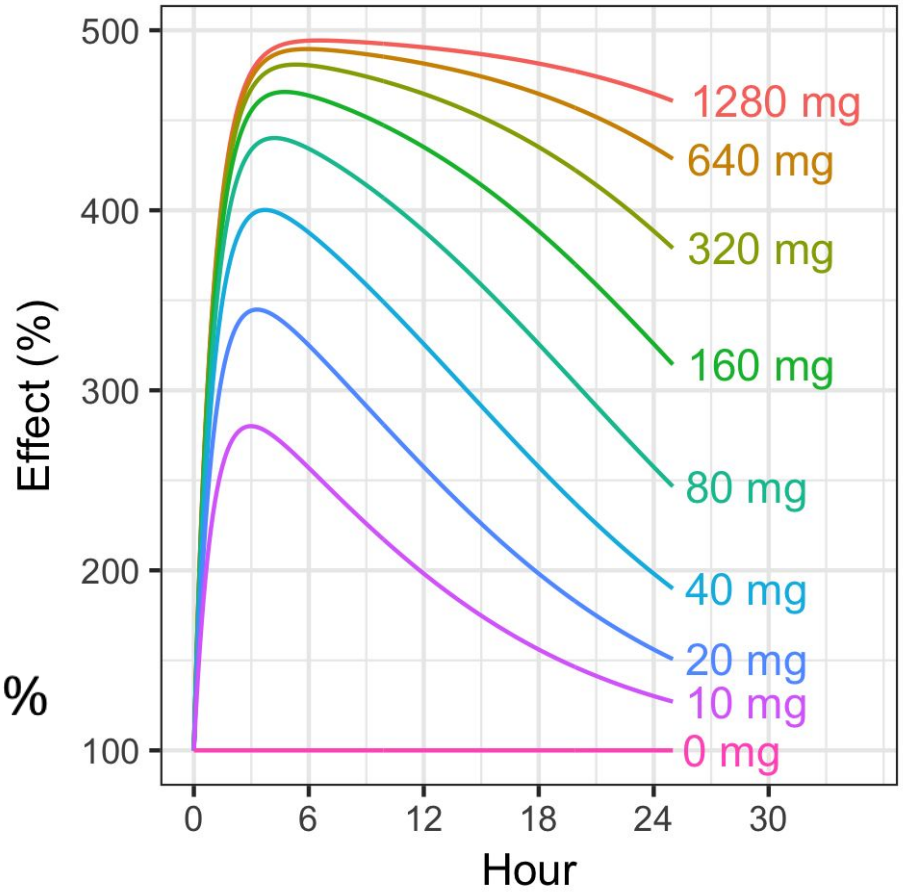


$$k_{in0} = 100\%/\text{h}$$
$$k_{out} = 1/\text{h}$$
$$E_{max} = 4$$
$$EC_{50} = 0.1\ \text{mg/L}$$

$$E_0 = \frac{k_{in0}}{k_{out}} = \frac{100\%/\text{h}}{1/\text{h}} = 100\%$$

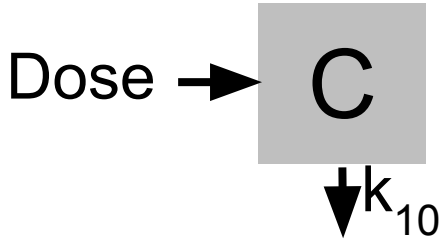
$$k_{in,max} = k_{in0}(1 + E_{max})$$
$$= 100\%/h(1 + 4) = 500\%$$

$$E_{ss,max} = \frac{k_{in,max}}{k_{out}} = \frac{500\%/h}{1/h} = 500\%$$



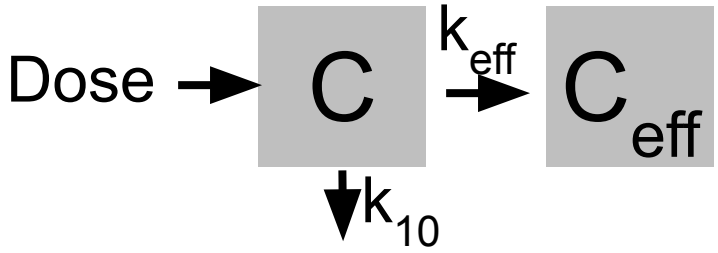
Overview – Drug effect/response

- Immediate



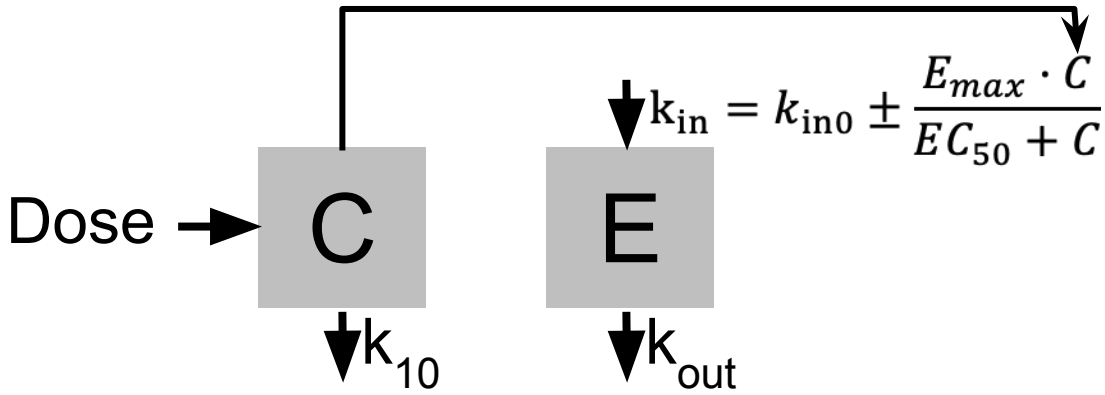
$$\text{Eff} = \frac{E_{max} \cdot C}{EC_{50} + C}$$

- Delayed
  - Distributional



$$\text{Eff} = \frac{E_{max} \cdot C_{\text{eff}}}{EC_{50} + C_{\text{eff}}}$$

- Cumulative
  - Tumor shrinkage
  - Bone remodeling



More complex models may be needed in some scenarios

- PD response changes with time. Examples include:
  - Tolerance, where first dose has larger effect than subsequent doses.
  - Cases where PD affects the PK
    - When a drug shrinks a tumor, but the tumor is also eliminating the drug.
    - When a drug that affects kidney function is also cleared by the kidney
    - When patient health generally affects clearance (e.g. checkpoint inhibitors)
- Data is rich enough and biology is well enough understood that more mechanism can be built into model

Key Lessons

- The Emax model is very useful for describing response
  - Emax = maximum effect
  - EC50 = concentration of 50% effect
  - γ = steepness of effect
- Model is inspired by physiology, but parameters do not always have direct physiological meaning
- Doubling dose of drug in general prolongs duration of effect by one half-life

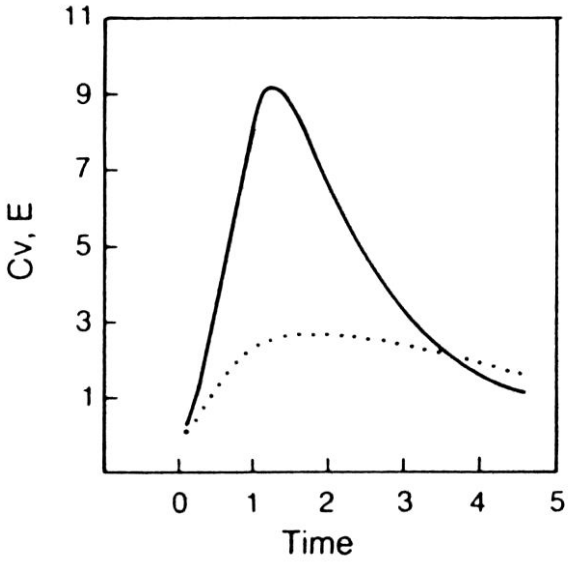
Where to learn more

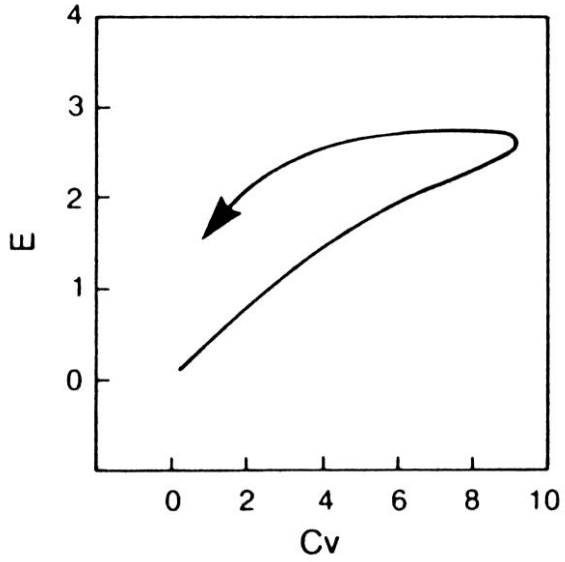
- Pharmacology and Pharmacokinetics
  - Rowland and Tozer, Clinical Pharmacokinetics and Pharmacodynamics (book)
- Pharmacometrics (Modeling)
  - Gabrielsson and Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis (book)
  - Bonate, Pharmacokinetic-Pharmacodynamic Modeling and Simulation (book)

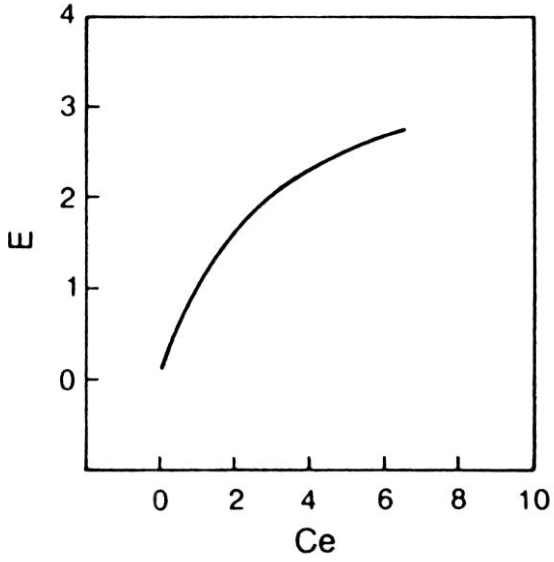
Bonus Topics

NOVARTIS

Counterclockwise hysteresis





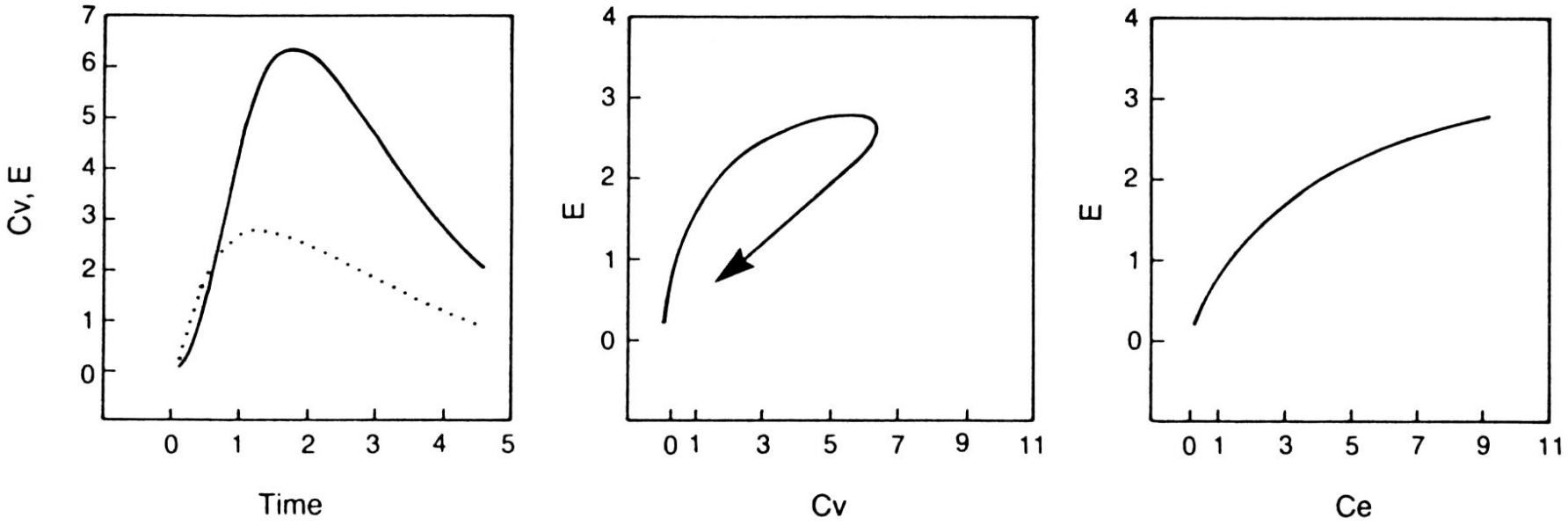


Reasons:
Biophase
Pro-drug
Indirect effect

Examples:
Anesthetics
Codeine
Cancer chemotherapy

Source: S Kern lecture

Clockwise hysteresis



Reasons:
Tolerance
Learning
Antagonistic metabolite

Examples:
Chronic activator/blocker
Antibiotics
Morphine (?)

Source: S Kern lecture