A cohesive model framework of receptor pharmacology: beyond the E_{max} model

Xiao Zhu[1], David Finlay[2], Michelle Glass[2], Stephen Duffull[1]

[1] School of Pharmacy, University of Otago, Dunedin, New Zealand

[2] Department of Pharmacology and Toxicology, University of Otago, Dunedin, New Zealand

A familiar equation

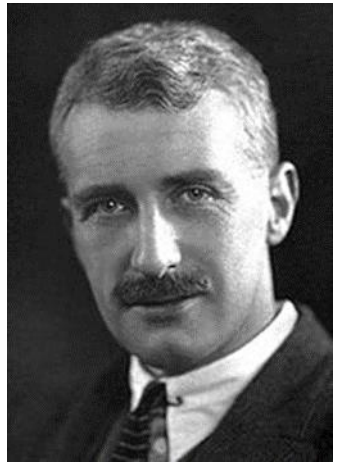
$$y = \frac{a \cdot x}{b + x}$$

Contains zero pharmacology

- Part of a large function class: rectangular hyperbolic function
- Curve features: monotonic and asymptotic
- This type of equation (and its variants) nearly always work to describe pharmacological data
- Interpretation of parameters may not be in accordance with underlying mechanisms
- Extrapolation to other settings is challenging and can possibly be wrong

Derivation of the E_{max} model

$$E = \alpha \cdot \varepsilon \cdot R_T \cdot \frac{C}{C + K_D} = E_{max} \cdot \frac{C}{C + C_{50}}$$



Archibald Vivian Hill

- Hill was the first to derive the E_{max}model and provide its biological interpretation
- Two independent parts: effect and binding
  - E_{max}(maximal effect): efficacy
    - α: scaling factor that converts receptor unit into effect unit
    - ε: intrinsic efficacy
    - R_T: total receptor
  - C_{50} (drug concentration at half maximal effect): potency
    - K_D: equilibrium dissociation constant

Hill, A. V. J Physiol. 1909; 39(5): 361-373

The E_{max} model is used ubiquitously

- The most widely used drug effect model in PD modelling
  - Effect compartment model
  - Indirect response model
  - Various kinds of mechanistic PD models
- Describe drug-receptor interactions (normally) at the level of a bioassay response
- So ingrained that assumptions attached to it are often overlooked

Aims

- To identify the assumptions underpinning the E_{max} model
- To relax these assumptions to accommodate different experimental conditions and physiological behaviours of systems

Eight fundamental assumptions of the E_{max} model

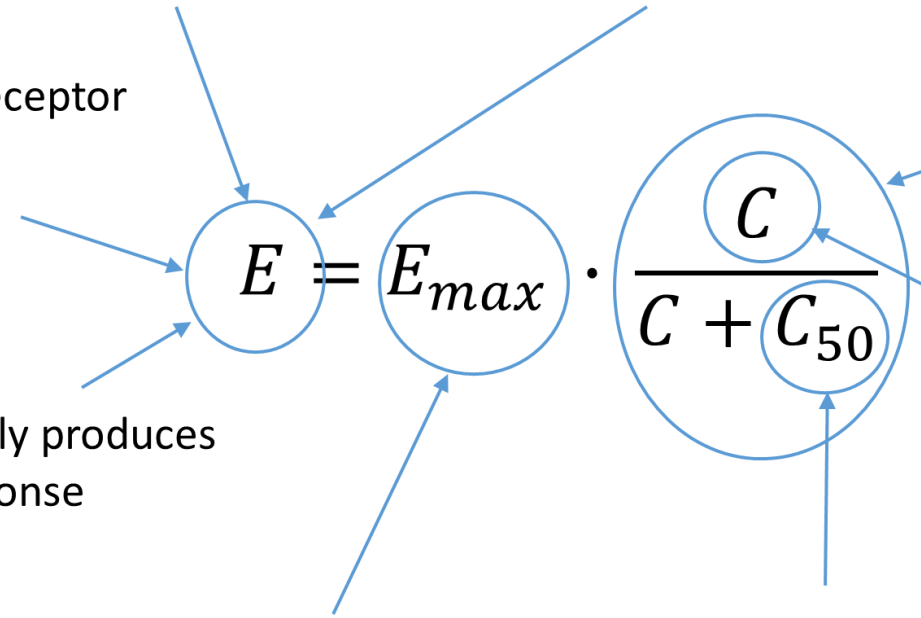
A.2 One receptor only has one binding site and can only form binary complex

A.1 Linear relationship between response and occupied receptor

$$E \propto CR$$

A.3 Only occupied receptor has response

$$E(C = 0) = 0$$



A.0 Law of mass action

A.4 One receptor only produces one type of response

A.7 Constant free drug

$C(t) = C$ for all t

A.5 Constant receptor number

$$E_{max} \propto R_T$$

A.6 Equilibrium binding

Two assumptions I will talk about today

A.2 One receptor only has one binding site and can only form binary complex

A.1 Linear relationship between response and occupied receptor

$E \propto CR$

A.3 Only occupied receptor has response

$E(C = 0) = 0$

A.0 Law of mass action

$$E = E_{max} \cdot \frac{C}{C + C_{50}}$$

A.4 One receptor only produces one type of response

A.7 Constant free drug

$C(t) = C$ for all t

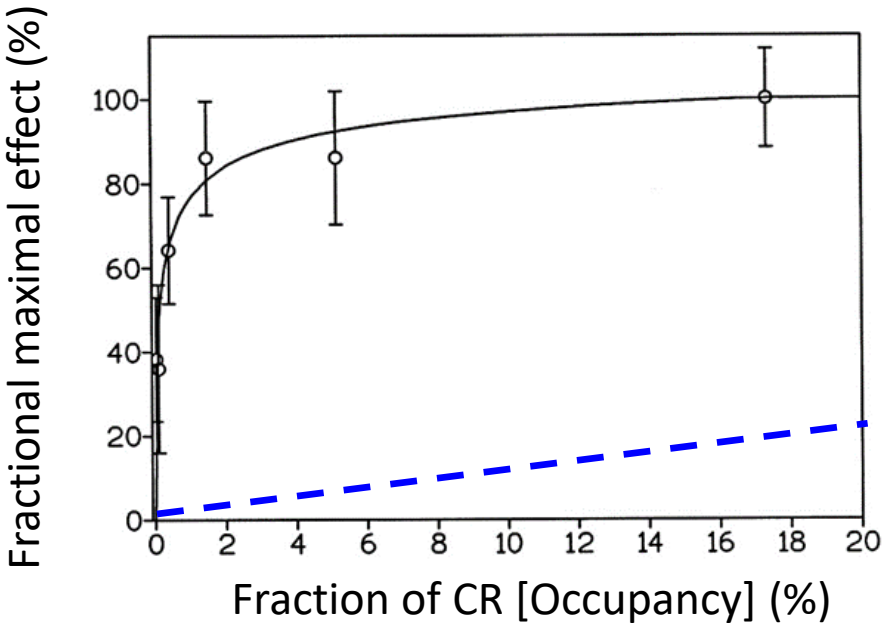
A.5 Constant receptor number

$E_{max} \propto R_T$

A.6 Equilibrium binding

Linear signalling assumption(A.1) may not hold

- Violation of linear signalling assumption (**A.1**)



- Maximal response with only a fraction of the receptor occupied

Gifford et al. J Pharmacol Exp Ther, 1999, 288(2): 478-483

Operational model: relaxation of A.1

- Black & Leff (1983) introduced an idea of "Transducer Function": *E=f(CR)*, and suggested *f(CR)* = E_{max} *model* (*i.e.*, **Operational Model**).

A.1	$E \propto CR$	Linear signalling
A.1'	$E \propto \frac{CR}{CR + K_E}$	Nonlinear signalling

Black JW, Leff P. Proc R Soc Lond B Biol Sci. 1983;220(1219):141-62

Operational model: E_{max} within an E_{max}

- Now we have two E_{max} models:

$$CR = R_T \cdot \frac{C}{C + K_D} \quad + \quad E = E_m \cdot \frac{CR}{CR + K_E}$$

E_m: system maximal effect

- Operational model:

$$E = \frac{E_m \cdot \frac{R_T}{K_E} \cdot C}{C \cdot \left(\frac{R_T}{K_E} + 1\right) + K_D} = \frac{E_m \cdot \tau \cdot C}{C \cdot (\tau + 1) + K_D}$$

Operational model vs. the E_{max} model

- The operational model can be re-parameterised into the E_{max} model, but will have different interpretation

$$E = \frac{E_m \cdot \tau \cdot C}{C \cdot (\tau + 1) + K_D} = \frac{E_m \cdot \tau}{\tau + 1} \cdot \frac{C}{C + \frac{K_D}{\tau + 1}} = E_{max} \cdot \frac{C}{C + C_{50}}$$

- E_{max} and C_{50} are always correlated

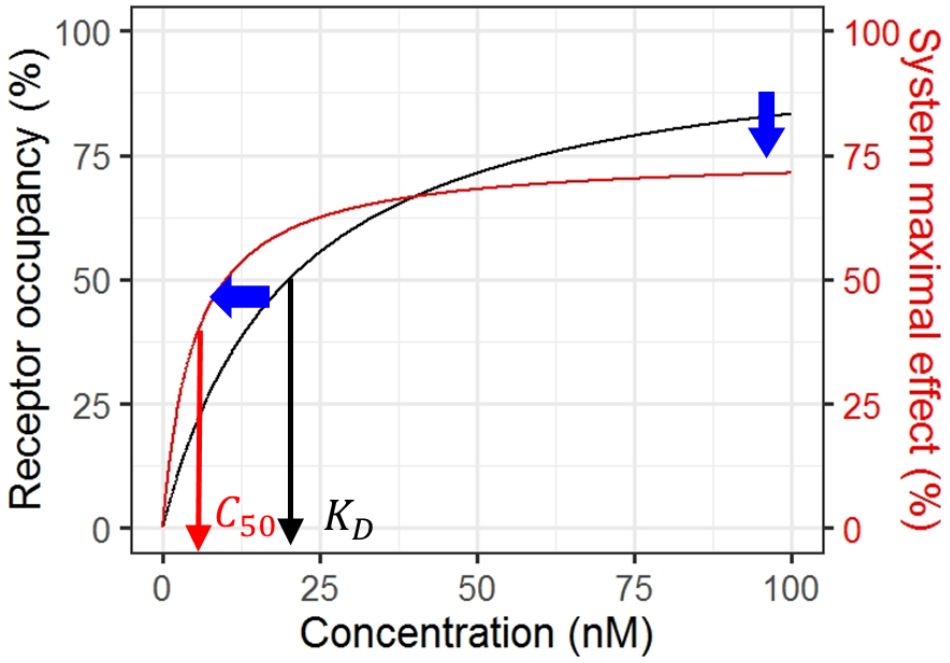
$$E_{max} = \frac{E_m \cdot \tau}{\tau + 1} \qquad C_{50} = \frac{K_D}{\tau + 1}$$

E_m: system parameter
K_D: ligand parameter
τ: system/ligand parameter

- E_{max} and C_{50} depend on both the system and the ligand

Operational model: cascade amplification

- The observed effect reaches the maximum much faster than receptor occupancy
- The maximum is now slightly lower after signal transduction

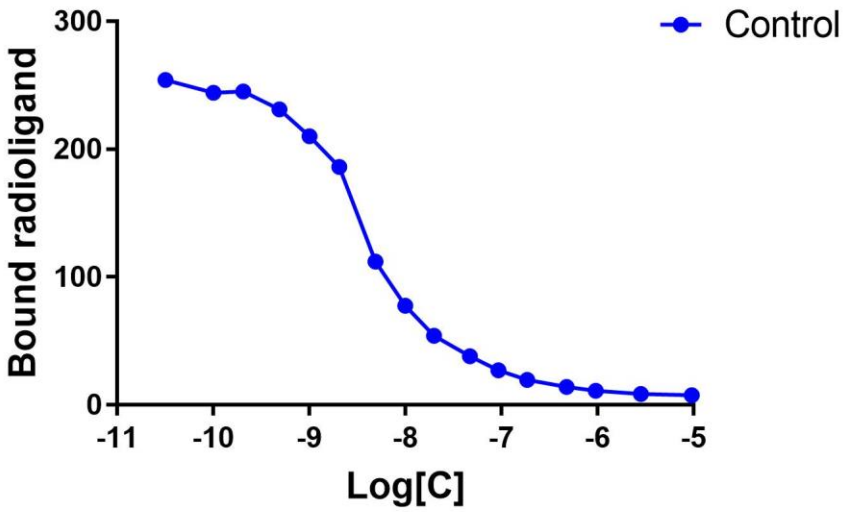


$$\frac{E_{max}}{E_m} = \frac{\tau}{\tau + 1} < 1$$

$$C_{50} = \frac{K_D}{\tau + 1} < K_D$$

Binary complex assumption(A.2) may not hold

- Violation of binary complex assumption (**A.2**)

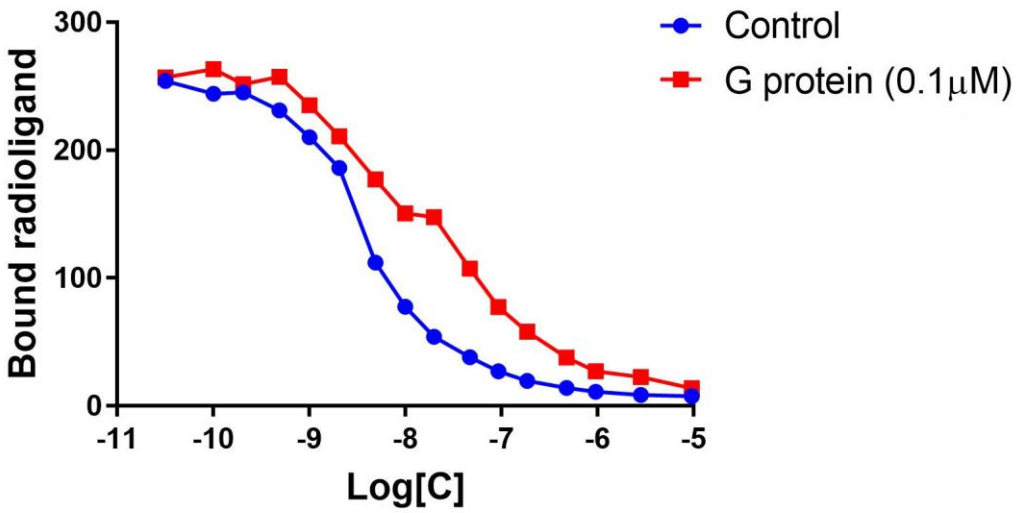


- An external protein (*e.g.,* G protein) could affect the affinity of agonists and the sensitivity of the system.

Adapted from De Lean et al. J Biol Chem. 1980;255:7108-7117

Binary complex assumption(A.2) may not hold

- Violation of binary complex assumption (**A.2**)

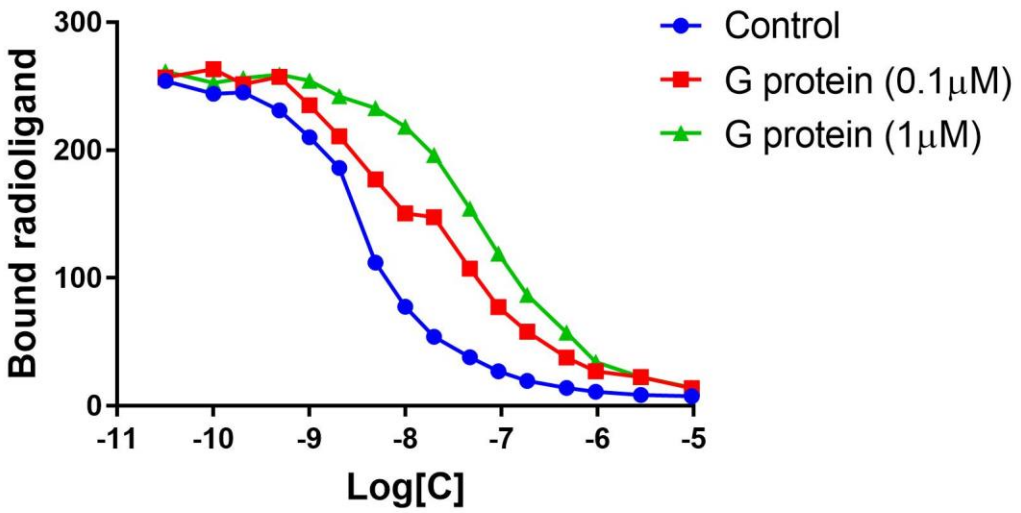


- An external protein (*e.g.,* G protein) could affect the affinity of agonists and the sensitivity of the system.

Adapted from De Lean et al. J Biol Chem. 1980;255:7108-7117

Binary complex assumption(A.2) may not hold

- Violation of binary complex assumption (**A.2**)

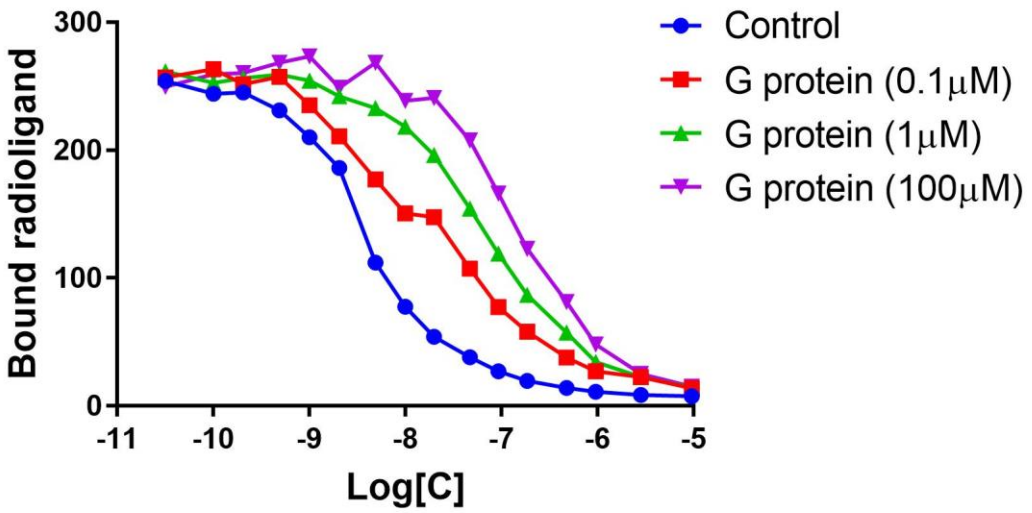


- An external protein (*e.g.,* G protein) could affect the affinity of agonists and the sensitivity of the system.

Adapted from De Lean et al. J Biol Chem. 1980;255:7108-7117

Binary complex assumption(A.2) may not hold

- Violation of binary complex assumption (**A.2**)

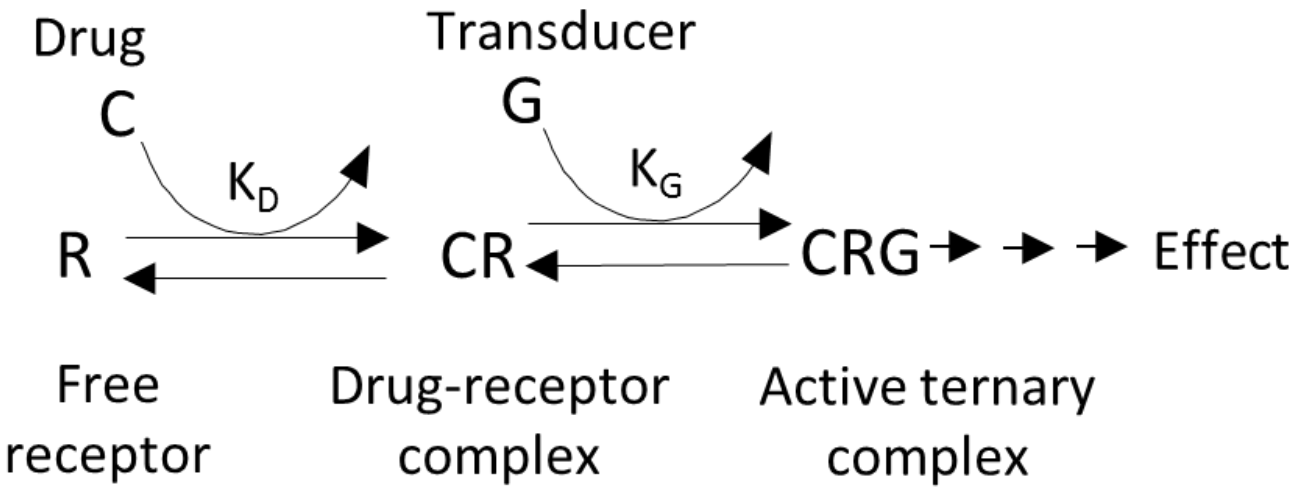


- An external protein (*e.g.,* G protein) could affect the affinity of agonists and the sensitivity of the system.

Adapted from De Lean et al. J Biol Chem. 1980;255:7108-7117

Ternary complex model: relaxation of A.2

- DeLean and colleagues first extended the E_{max} model to describe such systems by explicitly allowing the co-binding and allosteric interaction with a third component on GPCRs (*i.e.,* ternary complex model)



De Lean et al. J Biol Chem. 1980;255:7108-7117

Ternary complex model

- A possible mechanistic interpretation of the operational model

$$E = \alpha \cdot CRG = \frac{E_m \cdot \tau \cdot C}{C \cdot (\tau + 1) + K_D}$$

- When G protein is much less than receptor:

$$E_m = \alpha \cdot G_T \qquad \tau = \frac{R_T}{K_G}$$

- When G protein is much more than receptor:

$$E_m = \alpha \cdot R_T \qquad \tau = \frac{G_T}{K_G}$$

Ternary complex model vs. the E_{max} model

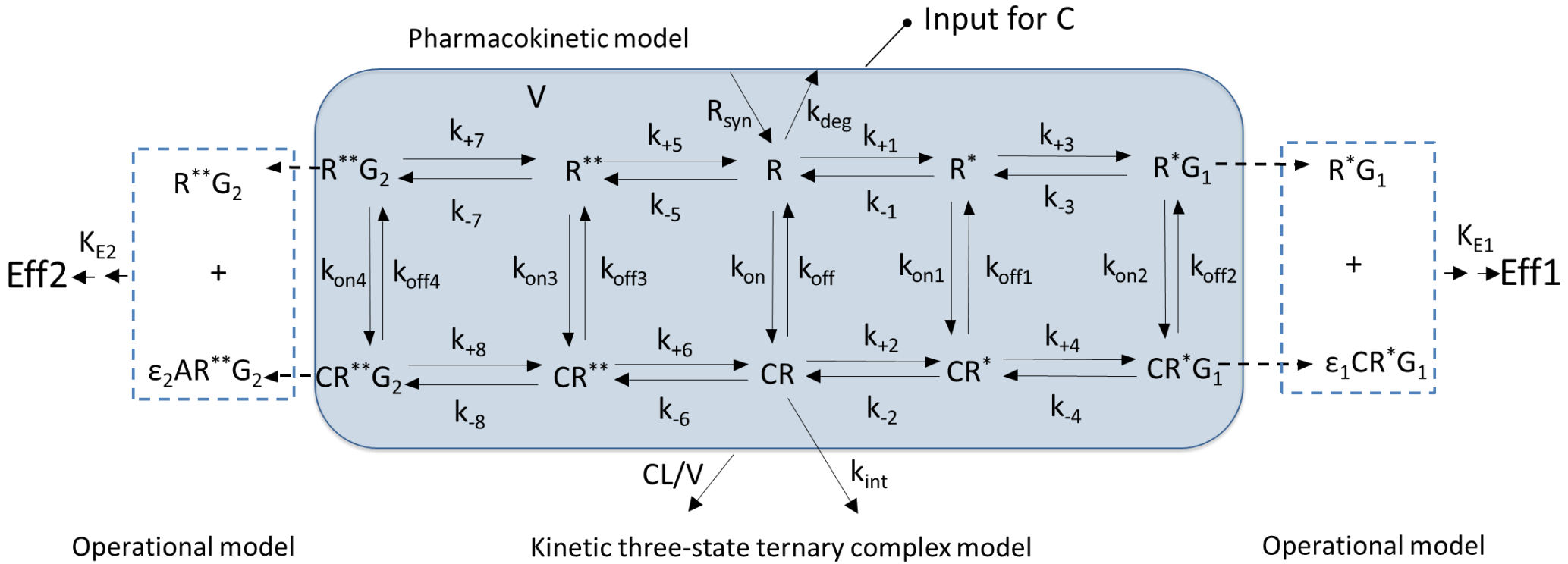
- Can be re-parameterised into E_{max} model

$$E_{max} = \frac{E_m \cdot \tau}{\tau + 1} \qquad C_{50} = \frac{K_D}{\tau + 1}$$

- The dependences of the curve change with the ratio of G protein to receptor
- When G protein is much less than receptor:
  - G protein only affects E_{max}
- When G protein is much more than receptor:
  - G protein affects both E_{max} and C_{50}

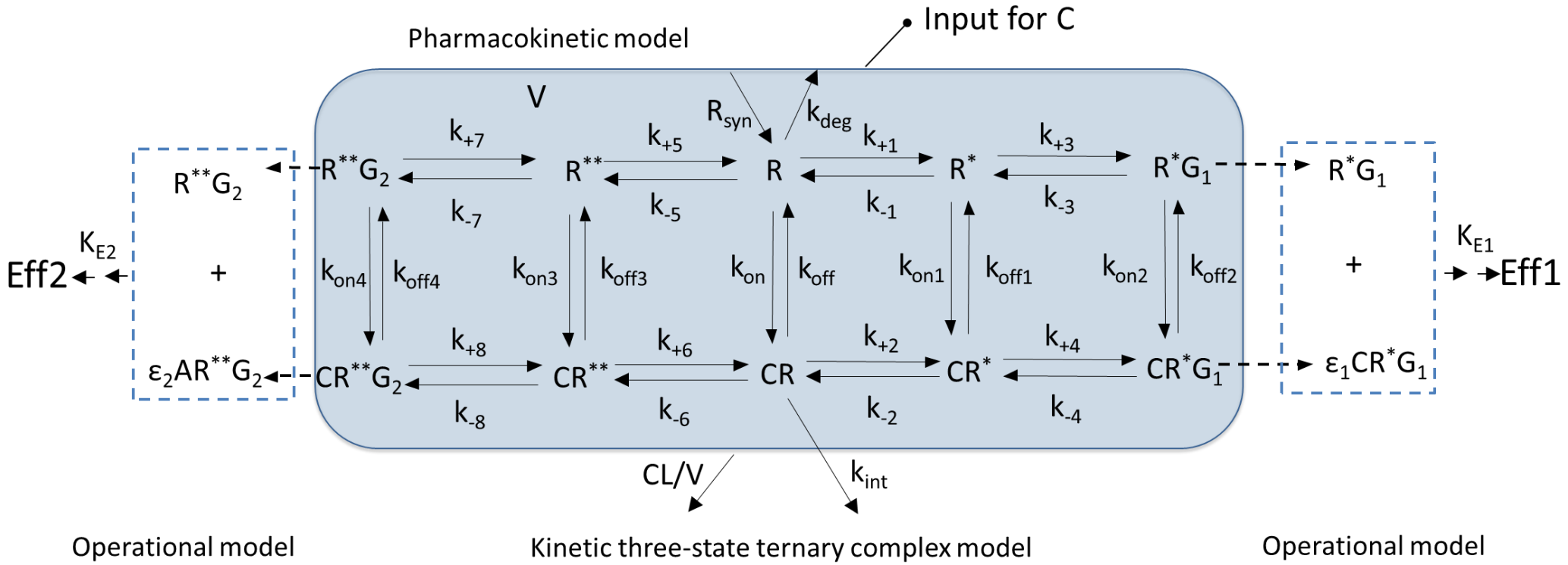
A cohesive model framework: relaxation of A.1-7

- Relax **A.1**-**A.7**: nonlinear signalling + allosteric modulation + constitutive activity + functional selectivity + receptor kinetics + binding kinetics + pharmacokinetics



Operational model always works

- Under equilibrium conditions, the operational model can describe the effect in each pathway, but the mechanism is lost



Inferences

- We never actually fit the E_{max}model we always fit the **Operational Model**
- All E_{max} models used are re-parameterisations of the **Operational Model**
- E_{max} and C_{50} are always naturally correlated
- The classic concepts of ‘full agonism’ and ‘partial agonism’ become blurred because E_{max} depends on both the system and the ligand

Acknowledgements

- University of Otago Doctoral Scholarship
- School of Pharmacy, University of Otago
- Otago Pharmacometrics Group