

# DIVERSE INDIRECT RESPONSE MODELS: THEORY

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## REVERSIBLE

### DIRECT

CNS  
Cardiovascular  
Muscle relaxation  
Enzyme Activity

### INDIRECT

Synthesis, Secretion  
Mediator Flux  
Cell Trafficking  
Enzyme Induction

## IRREVERSIBLE

Chemotherapeutic  
Enzyme Inactivation  
Reactive Metabolites  
Carcinogenicity

## Types of Effects

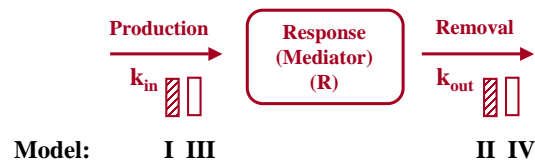
“A number of drugs induce effects not because of an interaction with receptors related to the effector, but on the strength of endogenous compounds.”

i.e. via their

- Protection
- Release

E.J. Ariëns, *Molecular Pharmacology*, 1964.

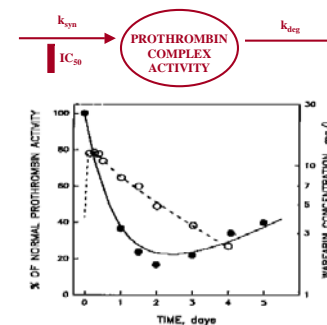
## Basic Indirect Response Models



Basic scheme for conceptualization of Indirect Reversible Effects. The time pattern of the mediator or response variable (R) is affected by drugs which can alter the production ( $k_{in}$ ) or dissipation ( $k_{out}$ ) process normally controlling endogenous levels of R. Drugs can inhibit or stimulate any of these processes.

Dayneka N, Garg V, Jusko WJ, *JPB* 21:457 (1993).  
Jusko and Ko, *CPT* 56:406 (1994).  
Sharma and Jusko, *BJCP* 45:229 (1998).

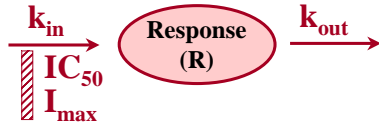
## Example of Inhibition of $k_{in}$



G. Levy

The first PK/PD analysis of IDR data was carried out by Nagashima et al (*Clin. Pharmacol. Ther.* 10: 22, 1969) who characterized Prothrombin Complex Activity (PCA) in blood (●) following oral doses (1.5 mg/kg) of warfarin (O, plasma concentrations). Warfarin inhibits Vitamin K-dependent synthesis of PCA and thus produces Model I behavior. Data reanalyzed by Jusko and Ko, *CPT* 56: 406 (1994).

## Model I: Symbols & Assumptions



$k_{in}$  - Zero-order production rate constant.

$k_{out}$  - First-order removal rate constant.

$R$  - Response variable with:

$R_0$  = Initial Value

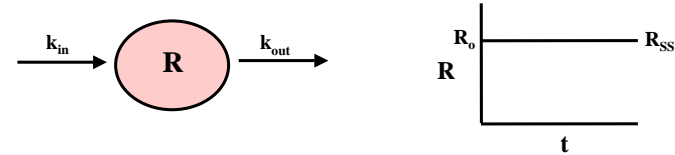
$R_m$  = Observed maximum response at each dose

$R_{max}$  = Maximum achievable response

$IC_{50}$  - Inhibition constant for 50% inhibition of maximum function of  $k_{in}$ .

$I_{max}$  - Maximum fractional (0→1) extent of inhibition.

## Baseline or Homeostasis: The System



$$\frac{dR}{dt} = k_{in} - k_{out} \cdot R \quad R(0) = R_0 = R_{SS}$$

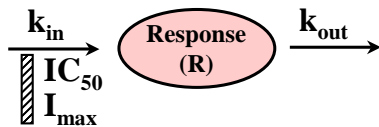
at SS:  $k_{in} - k_{out} \cdot R_0 = 0$

$$R_0 = \frac{k_{in}}{k_{out}}$$

Can be used to estimate  $k_{in}$  or  $k_{out}$  once other has been obtained.

$R_0$  may be set constant or be a fitted parameter.

## Indirect Response Model I



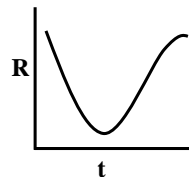
### 3 Components

Kinetics  
Pharmacology  
System

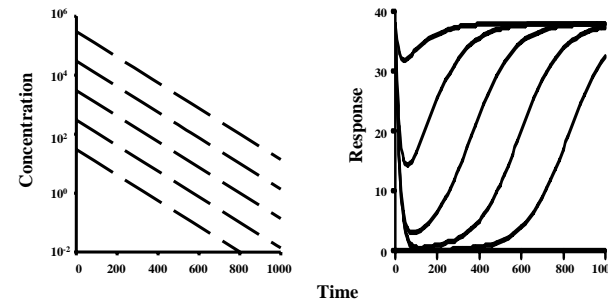
$$\frac{dR}{dt} = k_{in} \cdot \left( 1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p} \right) - k_{out} \cdot R$$

$$0 < I_{max} \leq 1$$

$$R(0) = R_0$$



## Temporal Response Patterns: Model I



### PK

- $V = 10000$
- $k_{el} = 0.01$
- Dose:  $\Delta 10$
- $C_p = D/V \cdot e^{-k_{el}t}$

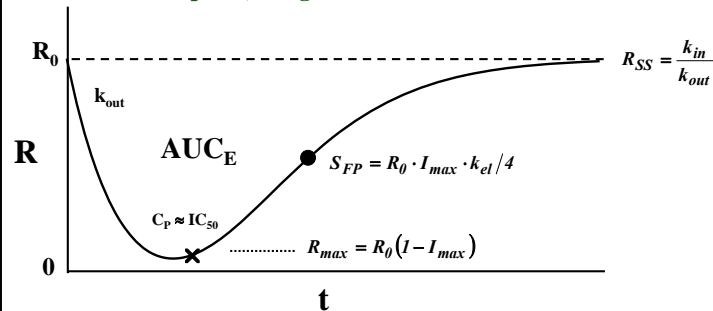
### PD

- $R_0 = 38$
- $k_{out} = 0.05$
- $I_{max} = 1$
- $IC_{50} = 100$

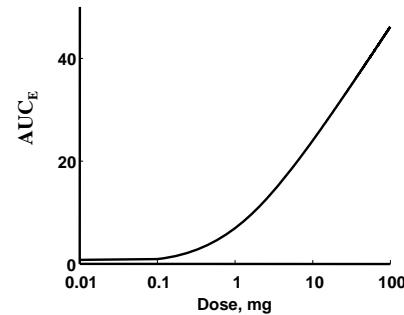
## Assess Properties of Function

$$\frac{dR}{dt} = k_{in} \left( 1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p} \right) - k_{out} \cdot R \quad R(0) = R_0$$

Examine limiting conditions, initial rates, peak/nadir, inflection point, integral.



## AUC<sub>E</sub>: IDR Model I



The DE are nonlinear and one cannot get convenient explicit solutions for R versus  $t$ . Must perform Numerical Integration.

$$AUC_E = R_0 \frac{I_{max}}{k_{el}} \ln \left( 1 + \frac{D/V}{IC_{50}} \right)$$

Krzyzanski & Jusko, *J. Pharm. Sci.* 87: 67 (1998).

Also termed "ABEC".

## Characteristics of Model I

- Steady-state :  $k_{in} = k_{out} \cdot R_0$
- Delay in  $T_{max}$
- $T_{max}$  increases with dose
- Large doses may attain  $R_{max}$  and extend duration of R
- Response dissipates at a zero-order rate
- $AUC_E$  is proportional to  $\ln$  Dose

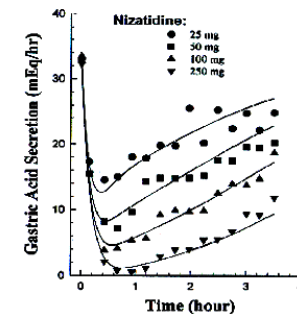
Common properties of drugs which have IDR according to Model I where drug is given as single IV doses.

## Estimation of Parameters

- $k_{out}$ : Initial decline phase ( $\ln$  scale,  $I_{max} = 1$ )
- $k_{in} = k_{out} \cdot R_0$
- $I_{max} : 1 - R_{max}/R_0$
- $IC_{50} : C_m \frac{R_m - R_0(1 - I_{max})}{R_0 - R_m}$

NB:  $C_m = C_p$  at  $R_m$

Procedure for examination of experimental data for estimating pharmacodynamic parameters.



Sharma A and Jusko WJ, *Brit. J. Clin. Pharmacol.* 45: 229 (1998).

## Model Definition: Assess

- Baseline pattern
- One dose should attain  $R_{max}$
- 2 or 3 doses are needed to discern model type and parameters

Experimental conditions which are necessary to fully elucidate all parameters of IDR.

Computer fitting with use of differential equations is necessary to obtain best parameter estimates.

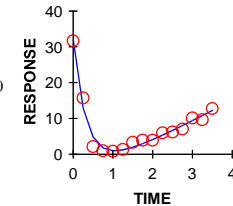
## WinNonlin Example

```

MODEL 1
TITLE
INDIRECT RESPONSE MODEL
COMMANDS
NFUN 1
NDER 1
NPAR 4
PNames 'kout','Ro','IC50','Imax'
NSEC 1
SNames 'kin'
END
TEMPORARY
T=X
Dose= 250000
V= 84
CL=46
kin=Ro^kout
C=Dose/V*EXP(-CL/V*T)
IHF=Imax*C/(C+IC50)
END
    
```

```

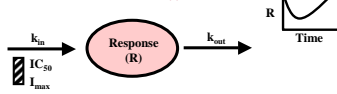
START
Z(1) = Ro
END
DIFFERENTIAL
DZ(1) = kin*(1-IHF)-kout*Z(1)
END
FUNCTION 1
F= Z(1)
END
SECONDARY
kin=Ro^kout
END
EOM
    
```



Parameter	Estimate	Standard Error
KOUT	4.55	1.06
RO	32.64	2.32
IC50	210.6	96.05
IMAX	0.999	0.078

## Family of Indirect Response Models

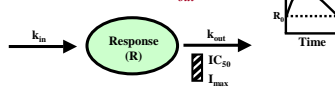
### I. INHIBITION - $k_{in}$



$$\frac{dR}{dt} = k_{in} \left( 1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p} \right) - k_{out} \cdot R$$



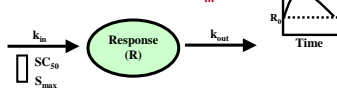
### II. INHIBITION - $k_{out}$



$$\frac{dR}{dt} = k_{in} - k_{out} \left( 1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p} \right) \cdot R$$



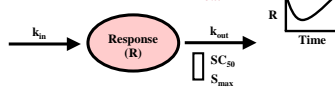
### III. STIMULATION - $k_{in}$



$$\frac{dR}{dt} = k_{in} \left( 1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p} \right) - k_{out} \cdot R$$



### IV. STIMULATION - $k_{out}$



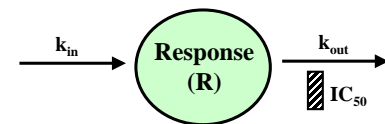
$$\frac{dR}{dt} = k_{in} - k_{out} \left( 1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p} \right) \cdot R$$



Sharma and Jusko, Br. J. Clin. Pharmacol. 45: 229 (1998)

## Indirect Response Model II:

Scheme and differential equation for Model II reflecting inhibition of  $k_{out}$  by drug concentrations ( $C_p$ ) with maximum inhibition of  $I_{max}$  and 50% inhibition at  $C_p = IC_{50}$ .  $I_{max}$  can range from 0 to 1.0.

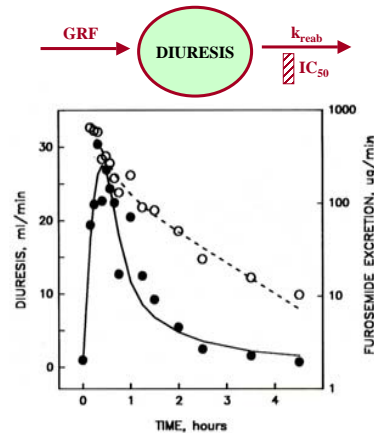


$$\frac{dR}{dt} = k_{in} - k_{out} \left( 1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p} \right) \cdot R$$

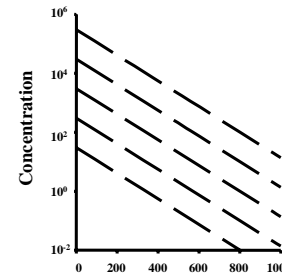
$$R(0) = R_0 \quad 0 < I_{max} \leq 1$$

## Example for IDR Model II:

Example of application of Model II. Diuretic effect (●) of furosemide following IV injection where  $k_{in} = \text{GFR}$ . Urinary excretion rates (○) were used as biophase concentrations because drug inhibits sodium reabsorption in the renal tubules. The data are from Alvan et al (*Clin. Pharmacol. Ther.* 29: 215, 1990) fitted with Model II by Jusko and Ko, *CPT* 56: 406 (1994).

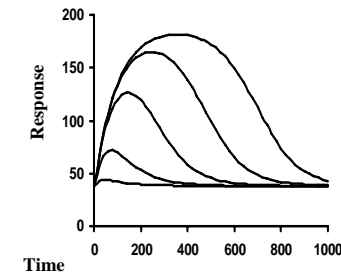


## Temporal Response Patterns: Model II



**PK**

- $V = 10000$
- $k_{el} = 0.01$
- Dose:  $\Delta 10$



**PD**

- $R_0 = 38$
- $k_{out} = 0.05$
- $I_{max} = 0.8$
- $IC_{50} = 100$

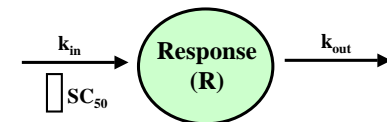
## Parameter Estimates: Model II

- $I_{max} = 1 - R_0/R_{max}$
- Initial Slope =  $k_{in} \cdot I_{max}$
- $k_{out} = k_{in}/R_0$
- $IC_{50} = C_m \frac{R_0 - R_m(1 - I_{max})}{R_m - R_0}$

Parameter estimates are more difficult to obtain from data when Model II is applicable.

## Indirect Response Model III:

Scheme and differential equation for Model III reflecting stimulation of  $k_{in}$  by drug concentrations ( $C_p$ ) with maximum stimulation of  $S_{max}$  and 50% stimulation at  $C_p = SC_{50}$ .  $S_{max}$  can be any positive value.

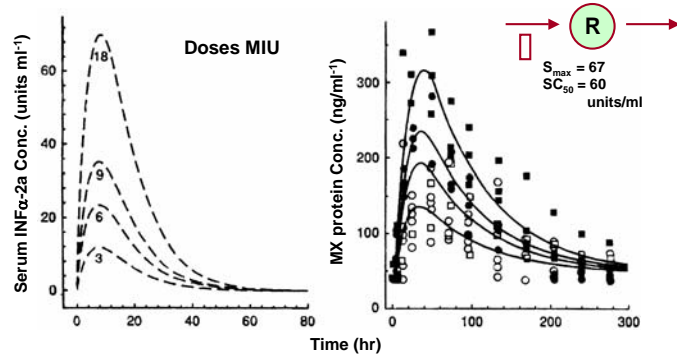


$$\frac{dR}{dt} = k_{in} \left( 1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p} \right) - k_{out} \cdot R$$

$$R(0) = R_0 \quad S_{max} > 0$$

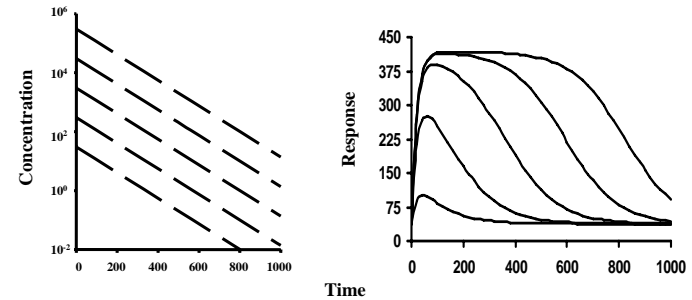
## Example for IDR Model III:

Nieforth et al, *Clin. Pharmacol. Ther.* 59: 636 (1996).



Pharmacokinetics and Pharmacodynamics (Increase of Blood MX Protein Concentrations) of Interferon Alpha-2a After the Single Subcutaneous Administration of the Indicated Doses in Normal Volunteers.

## Temporal Response Patterns: Model III



**PK**

- $V = 10000$
- $k_{el} = 0.01$
- Dose:  $\Delta 10$

**PD**

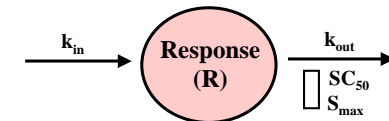
- $R_0 = 38$
- $k_{out} = 0.05$
- $S_{max} = 10$
- $SC_{50} = 100$

## Parameter Estimates: Model III

- $S_{max} = (R_{max}/R_0) - 1$
- Initial slope =  $k_{in} \cdot S_{max}$
- $k_{out} = k_{in}/R_0$
- $SC_{50} = C_m \frac{R_m - R_0(1 - S_{max})}{R_0 - R_m}$

## Indirect Response Model IV:

Scheme and differential equation for Model IV showing stimulation of  $k_{out}$  by drug concentrations ( $C_p$ ) with maximum stimulation of  $S_{max}$  and 50% stimulation at  $C_p = SC_{50}$ .  $S_{max}$  can be any positive value.

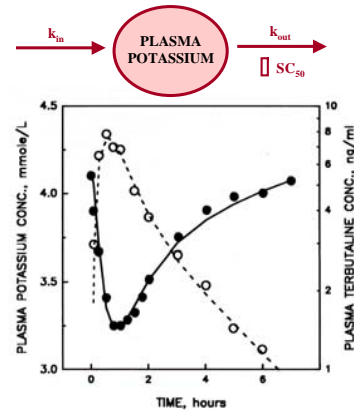


$$\frac{dR}{dt} = k_{in} - k_{out} \left( 1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p} \right) \cdot R$$

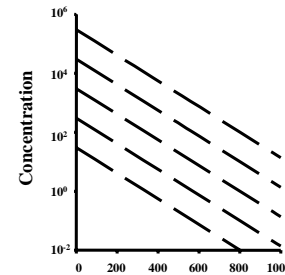
$$R(0) = R_0 \quad S_{max} > 0$$

## Example for IDR Model IV:

Example of application of Model IV. Terbutaline plasma concentrations (●) cause efflux of plasma potassium (○) into tissues. The data are from Jonkers et al (*Clin. Pharmacol. Ther.* 42: 627, 1987) and were fitted using Model IV by Jusko and Ko, *CPT* 56: 406 (1994).

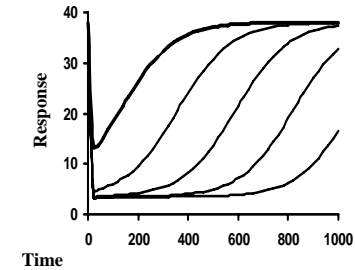


## Temporal Response Patterns: Model IV



### PK

- $V = 10000$
- $k_{el} = 0.01$
- Dose:  $\Delta 10$



### PD

- $R_0 = 38$
- $k_{out} = 0.05$
- $I_{max} = 1$
- $IC_{50} = 100$

## Parameter Estimates: Model IV

- $S_{max} = R_0 / R_{max} - 1$
- Initial slope =  $-k_{in} \cdot S_{max}$
- $k_{out} = k_{in} / R_0$
- $SC_{50} = C_m \frac{R_0 - R_m (1 - S_{max})}{R_m - R_0}$

## Indirect Response Models May be Relevant for:

	<u>Model</u>		<u>Model</u>
Anticoagulant agents	I	Cholinesterase inhibitors	II
Corticosteroids (Adrenal suppression)	I	Diuretics	II
Corticosteroids (Cell trafficking)	I	Corticosteroids (Cell trafficking)	II
H <sub>1</sub> - antagonists	I	Uricosuric agents	II
H <sub>2</sub> - antagonists	I	GABA Inhibitors	II
Antipyretic agents	I	Dopamine antagonists	III
ACE inhibitors	I	Enzyme inducers	III
5 $\alpha$ -Reductase inhibitors	I	$\beta$ -Agonists (Bronchodilation)	III
Aldose reductase inhibitors	I	Oral hypoglycemic agents	I, IV
LH Antagonists	I	$\beta$ -Agonists (Hypokalemia)	IV
Thromboxane Synthase inhibitors	I	Insulin Sensitizers (PPAR $\gamma$ )	IV

... and many others

## Basic Indirect Response Models



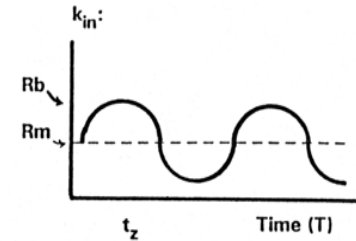
Alterations can be made in:

- Input processes
  - Removal processes
  - Compartments
  - Nature of drug effects
- ...and many combinations

## Nonstationarity

### CIRCADIAN INPUT PROCESS

Many body functions such as hormone secretion, blood pressure, temperature, and renal function are governed by circadian rhythms. These can be modeled by considering  $k_{in}$  to be a cosine function where:



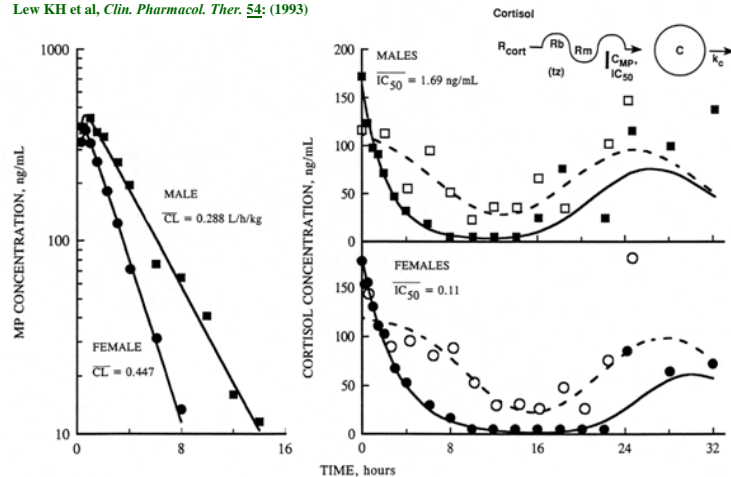
$R_m$  = mean input rate  
 $R_b$  = amplitude of input rate  
 $T$  = decimal clock time (24 hr clock)  
 $T_z$  = acrophase (peak) time  
 $2\pi/24$  = conversion of time to radians

$$k_{in} = R_m + R_b \cdot \cos [(T - t_z) \cdot 2\pi/24]$$

$$\frac{dR}{dt} = k_{in} \cdot I(t) - k_{out} \cdot R$$

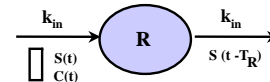
## Gender and Methylprednisolone PK/PD

Lew KH et al, *Clin. Pharmacol. Ther.* 54: (1993)



## Basic Pharmacodynamic Models For Agents Which Alter Production of Natural Cells: Application to Lenograstim

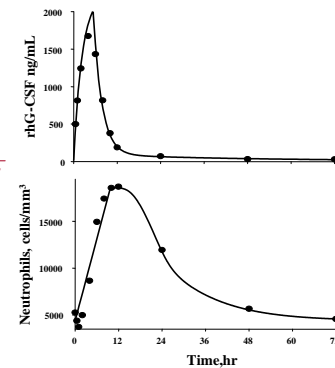
W. Krzyzanski, R. Ramakrishnan, and W. J. Jusko, *JPB*, 27: 467 (1999)



$$\frac{dR}{dt} = \frac{K_s C(t)^{\gamma}}{SC'_{50} + C(t)^{\gamma}} - \frac{K_s C(t - T_R)^{\gamma}}{SC'_{50} + C(t - T_R)^{\gamma}}$$

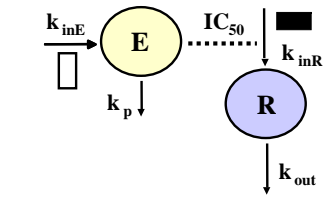
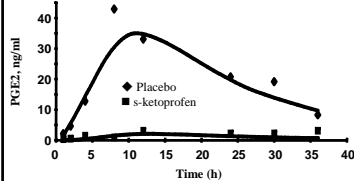
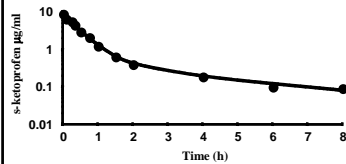
$$K_s = k_{in} \cdot S_{max}$$

**Assumption :** Each cell has a specific life span,  $T_R$ .



## Modeling of Provoked Responses: Inflammation

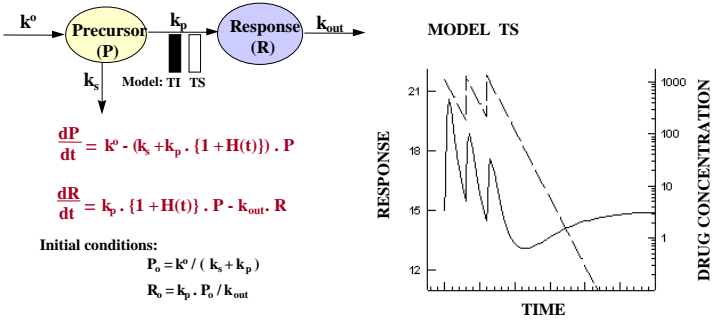
Lepist I, Jusko WJ, *J.Vet. Pharmacol. Therap.* 27: 211 (2004).  
 Related model: Gozzi et al, *JPET* 291: 199 (1999).



$$\frac{dE}{dt} = k_{inE} \cdot [0 - T] - k_p \cdot E, \quad E_0 = 0$$

$$\frac{dR}{dt} = k_{inR} \cdot \left( 1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p} \right) \cdot E - k_{out} \cdot R, \quad R_0 = 0$$

## Indirect Response Models With Precursor Compartment



$$\frac{dP}{dt} = k^0 - (k_s + k_p \cdot \{1 + H(t)\}) \cdot P$$

$$\frac{dR}{dt} = k_p \cdot \{1 + H(t)\} \cdot P - k_{out} \cdot R$$

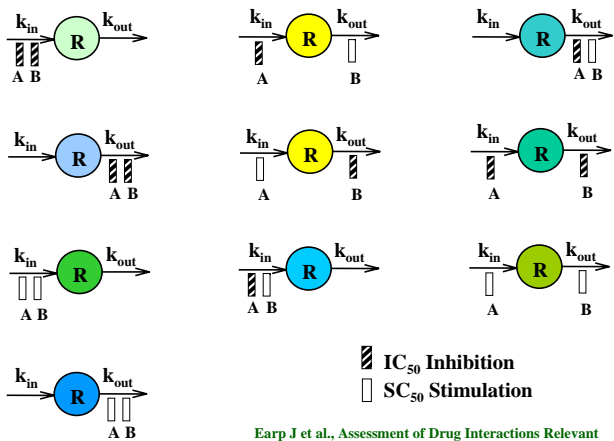
Initial conditions:  
 $P_0 = k^0 / (k_s + k_p)$   
 $R_0 = k_p \cdot P_0 / k_{out}$

And  $H(t)$  = Hill Function  

$$= \frac{S_{max} \cdot C_p}{SC_{50} + C_p} \text{ for Model TS}$$

A. Sharma, W.F. Ebling, and W.J. Jusko, Precursor-Dependent Indirect Response Model for Tolerance and Rebound Phenomena, *J. Pharm. Sci.* 87:1577 (1998).

## Drug Interactions: Indirect Responses



Legend:  
 ▨  $IC_{50}$  Inhibition  
 □  $SC_{50}$  Stimulation

Earp J et al., Assessment of Drug Interactions Relevant to Pharmacodynamic Indirect Response Models, *JPP* 31: 345 (2004).

## Summary: Indirect Response Models

- **IDR** account for the PK/PD of numerous drugs which inhibit or stimulate production or loss of the response variable.
- These models operate via differential equations with PK, mechanism (Hill Equation), and system (production/loss) components.
- Minimum parameters needed:  $I_{max}$  (or  $S_{max}$ ),  $IC_{50}$  (or  $SC_{50}$ ),  $k_{out}$
- The properties, similarities, and differences of the four basic IDR have been well characterized.
- The basic models can be extended to deal with various complexities.