

# TRANSDUCTION MODELS: THEORY

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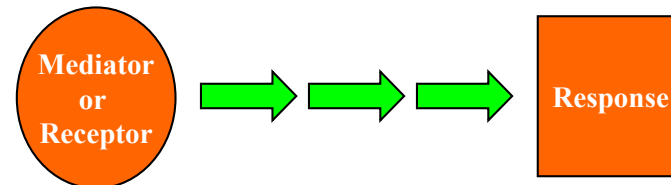


UNIVERSITY AT BUFFALO

State University of New York

ACCP 2006

## Modeling Signal Transduction in Pharmacodynamics

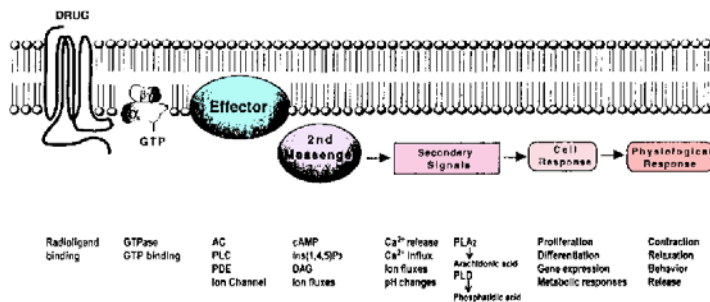


Transduction Processes can be rapid to slow, single to multiple, linear or nonlinear.

Approaches:

- Operational Model  
Black & Leff  
Danhof et al.
- Transit Compartment
- Complete Mechanisms

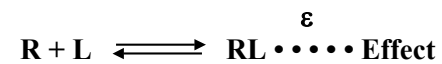
## Types of Signal Transduction



Harden TK et al, In:  
Leff P, Receptor-Based Drug Design,  
Marcel Dekker Inc, NY

## Intrinsic Activity: $\epsilon$

Ariens (1954), Stephenson (1956), Black & Leff (1983)



$\epsilon$  = proportionality constant between biological response and receptor occupancy.



Sir James Black

$$\frac{\text{Effect}}{E_{\max}} = \epsilon \cdot \frac{RL}{R_{\text{TOT}}} = \epsilon \cdot \frac{L}{K_D + L}$$

$\epsilon$  may be linear or nonlinear

## Operational Models of Pharmacological Agonism

J.W. Black and P. Leff, *Proc. R. Soc. Lond. B* 220: 141-162 (1983)

Drug-Receptor Binding

$$[AR] = \frac{[R_0] \times [A]}{K_A + [A]}$$

Transduction of Occupation into Response

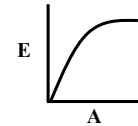
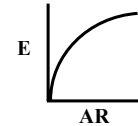
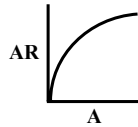
$\mathcal{E}$

$$\frac{E}{E_m} = \frac{[AR]^n}{K_E^n + [AR]^n}$$

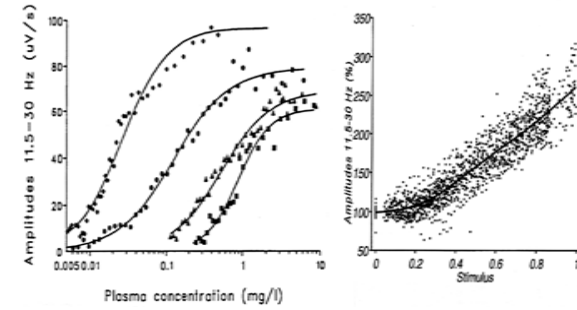
( $K_E$  = Transducer constant)

$$E = \frac{E_m \times \tau^n \times [A]^n}{(K_A + [A])^n + \tau^n \times [A]^n}$$

where Operational Efficacy,  $\tau$ , is defined as  $R_0/K_E$



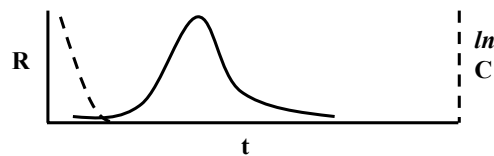
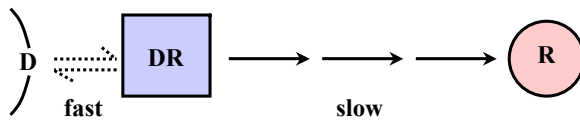
## Receptor Model for Concentration-effect Relationships Benzodiazepine Receptor Occupancy and EEG Effects



- Concentration-EEG effect relationship of the benzodiazepine agonists flunitrazepam (◆), midazolam (●), oxazepam (▲), and clobazam (■) in four rats. LHS shows best fits of the sigmoidal  $E_{max}$  model to the actual data. RHS shows Effects related to Fractional Receptor Occupancy where Stimulus =  $Conc/(K_D + Conc)$ .

From: Mandema et al, *J. Pharmacol. Exp. Ther.* 257: 472-478, 1991.

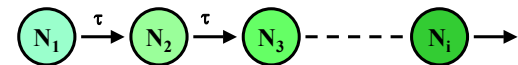
## Modeling Time-Dependent Transduction



Basic question: How to capture a response profile where transduction steps cause time delays?

Problem: No intermediary measurements.

## Gamma Distribution Function (Poisson)

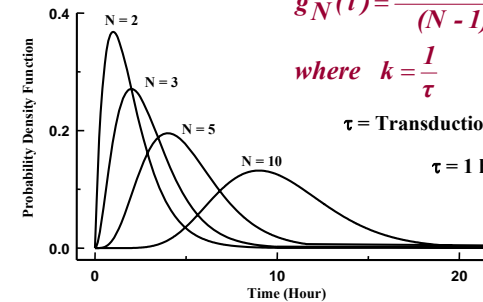


$$g_N(t) = \frac{k^N \cdot t^{N-1}}{(N-1)!} \cdot e^{-k \cdot t}$$

$$\text{where } k = \frac{1}{\tau}$$

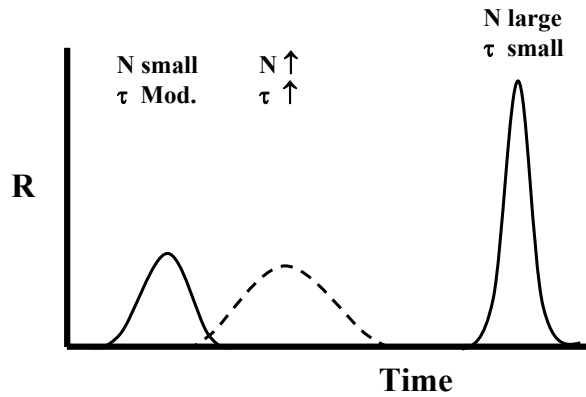
$\tau$  = Transduction Time

$\tau = 1 \text{ hr}$



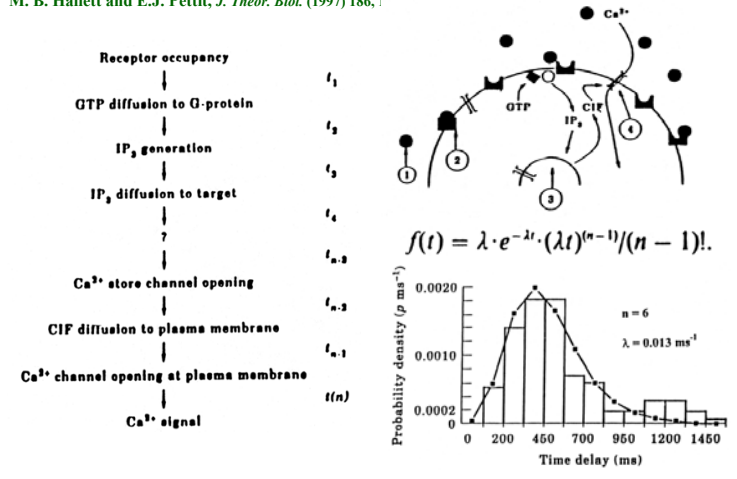
Assume: Unit dose input into  $N_1$

## Flexibility of Gamma Distribution Function



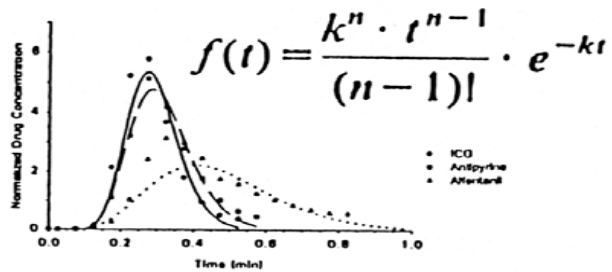
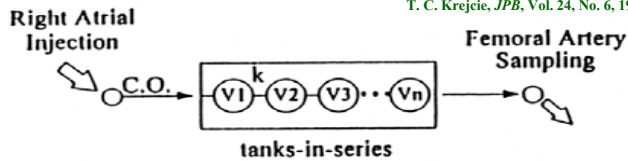
## Stochastic Events Underlie Ca<sup>2+</sup> Signaling in Neutrophils

M. B. Hallett and E.J. Pettit, *J. Theor. Biol.* (1997) 186,1

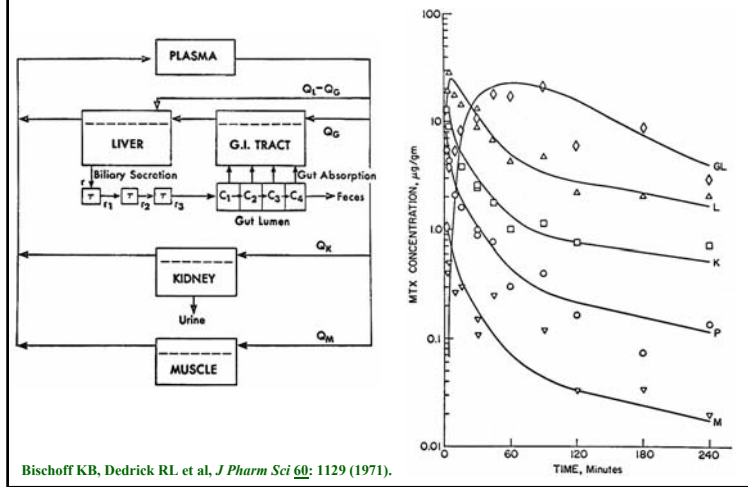


## Use of Parallel Erlang Density Functions First-Pass Pulmonary Uptake of Multiple Indicators in Dogs

T. C. Krejcie, *JPB*, Vol. 24, No. 6, 1996

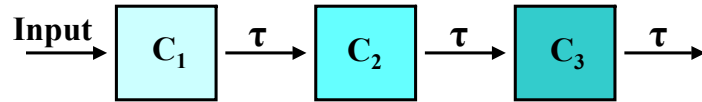


## PBPK Model for Methotrexate



Bischoff KB, Dedrick RL et al, *J Pharm Sci* 60: 1129 (1971).

## Transit Compartments for Time-Delays



$$\frac{dC_1}{dt} = \text{Input} - \frac{1}{\tau} \cdot C_1$$

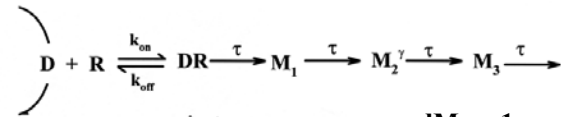
$$\frac{dC_2}{dt} = \frac{1}{\tau} \cdot C_1 - \frac{1}{\tau} \cdot C_2$$

$$\frac{dC_3}{dt} = \frac{1}{\tau} \cdot C_2 - \frac{1}{\tau} \cdot C_3 = \frac{1}{\tau} \cdot (C_2 - C_3)$$

$$\tau = \frac{1}{k}$$

(first-order constant)

## Signal Transduction Process Using Transit Compartments

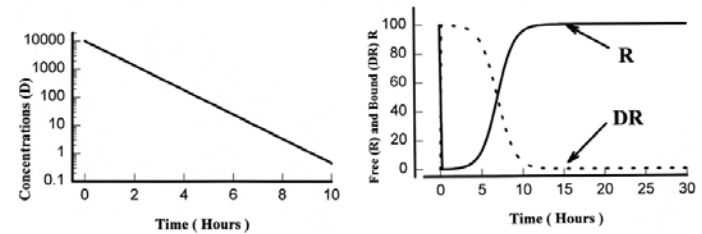


$$D = D_0 \cdot \exp^{-\lambda \cdot t}$$

$$\frac{dR}{dt} = -k_{\text{on}} \cdot D \cdot R + k_{\text{off}} \cdot DR$$

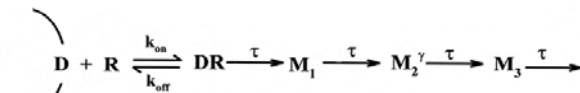
$$\frac{dDR}{dt} = k_{\text{on}} \cdot D \cdot R - k_{\text{off}} \cdot DR$$

$$\frac{dM_1}{dt} = \frac{1}{\tau} \cdot DR - \frac{1}{\tau} \cdot M_1$$



Sun Y-N and Jusko WJ, *J Pharm Sci* 87: 732 (1998).

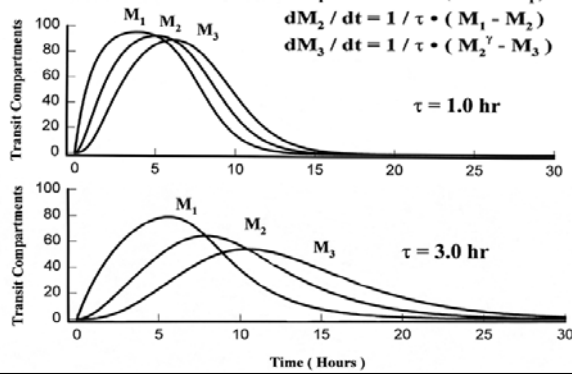
## Modeling Signal Transduction: Parameters $N$ , $\tau$ , $\gamma$



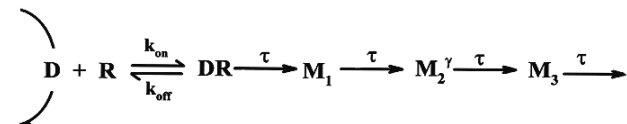
$$\frac{dM_1}{dt} = 1/\tau \cdot (DR - M_1)$$

$$\frac{dM_2}{dt} = 1/\tau \cdot (M_1 - M_2)$$

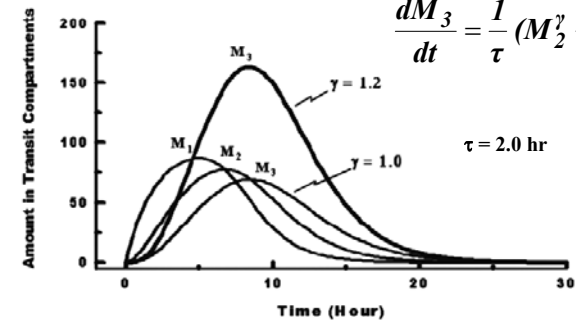
$$\frac{dM_3}{dt} = 1/\tau \cdot (M_2^\gamma - M_3)$$



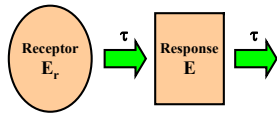
## Signal Amplification or Dampening: Use of $\gamma$



$$\frac{dM_3}{dt} = \frac{1}{\tau} (M_2^\gamma - M_3)$$



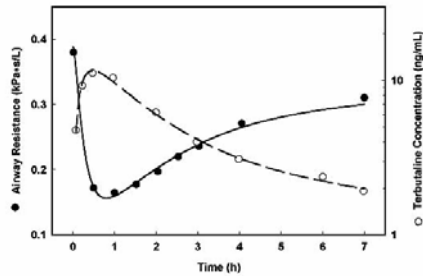
## Modeling Signal Transduction: One Step



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

$$\frac{dE}{dt} = \frac{1}{\tau} (E_r - E)$$

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

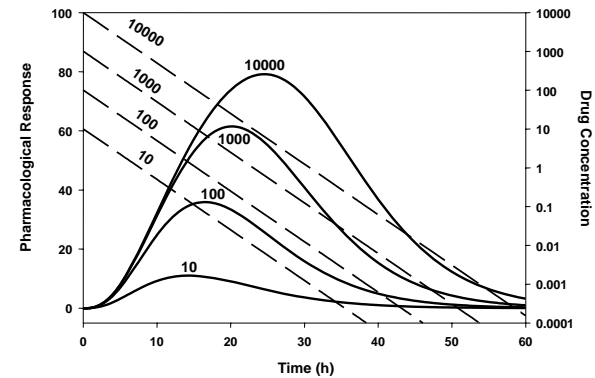
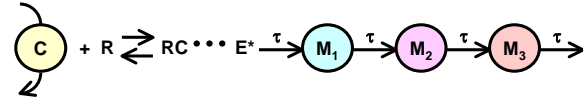


$$E_{max} = 0.38, \quad EC_{50} = 6.6 \text{ ng}/\mu\text{L},$$

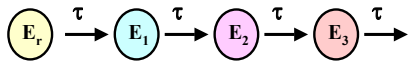
$$\tau = 0.18 \text{ h}, \quad E_0 = 0.39$$

Mager D and Jusko WJ, *CPT* 70: 210, 2001.

## PK/PD Profiles of Time-Dependent Transduction



## Modeling Signal Transduction: Several Steps

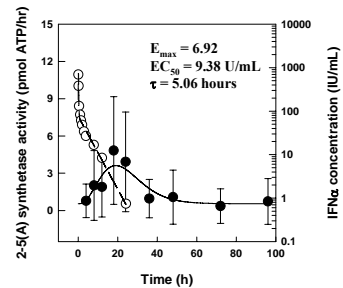


Equations:

$$\frac{dE_1}{dt} = \frac{1}{\tau} \left( \frac{E_{max} \cdot C}{EC_{50} + C} - E_1 \right)$$

$$\frac{dE_2}{dt} = \frac{1}{\tau} (E_1 - E_2)$$

$$\frac{dE_3}{dt} = \frac{1}{\tau} (E_2 - E_3)$$



$$E_{max} = 6.92$$

$$EC_{50} = 9.38 \text{ U/mL}$$

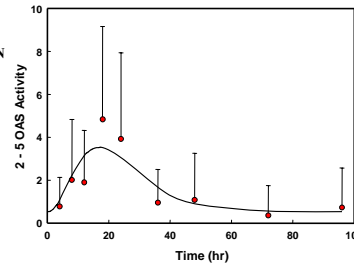
$$\tau = 5.06 \text{ hours}$$

Mager D and Jusko WJ, *Pharmacodynamic Modeling of Time-Dependent Transduction Systems, Clin. Pharmacol. Ther.* 70:210 (2001).

## WinNonlin Model for IFN $\alpha$ (Linear S)

```

MODEL
COMMANDS
NFUN 1
NDER 5
NPARAMETERS 3
PNAMES 'S','tau','Eo'
END
TEMPORARY
T=X
Dose=10000000
Tinf=10/60
k12 = 6.24
k21 = 0.693
kel = 2.61
Vc = 7234
IF T<Tinf THEN
  Ko=Dose/Tinf
ELSE
  Ko=0
ENDIF
END
START
Z(1)=0
Z(2)=0
Z(3)=0
Z(4)=0
Z(5)=0
END
DIFF
DZ(1) = Ko + k21*Z(2) - (kel+k12)*Z(1)
DZ(2) = k12*Z(1) - k21*Z(2)
DZ(3) = 1/tau*(S*Z(1)/Vc-Z(3))
DZ(4) = (Z(3)-Z(4))/tau
DZ(5) = (Z(4)-Z(5))/tau
END
FUNC 1
F= Eo + Z(5)
END
EOM
    
```



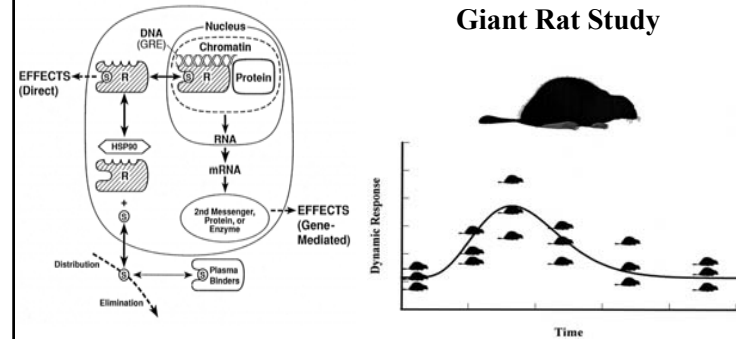
Parameter	Estimate	CV%
S	0.154	25
$\tau$	6.47	15
Eo	0.533	27

$$\frac{dE_1}{dt} = \frac{1}{\tau} (S \cdot C - E_1)$$

## Modeling Transduction Processes

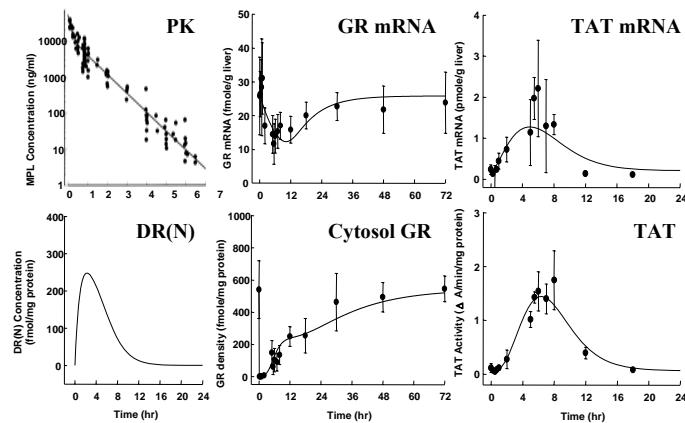
- **Black & Leff:** Need combined receptor and response data.
- **Transit Compartments:** Optimize search for  $N$  and  $\tau$  (and  $\gamma$ ) with  $dM_i/dt = (1/\tau)(M_{i-1} - M_i)$ .
- **Mechanistic Models:** Measure and include intermediary processes between PK and response.

## Fifth-Generation Model for Corticosteroid Pharmacodynamics: Application to Steady-State Receptor Down-Regulation and Enzyme Induction Patterns during Seven-Day Continuous Infusion of Methylprednisolone in Rats

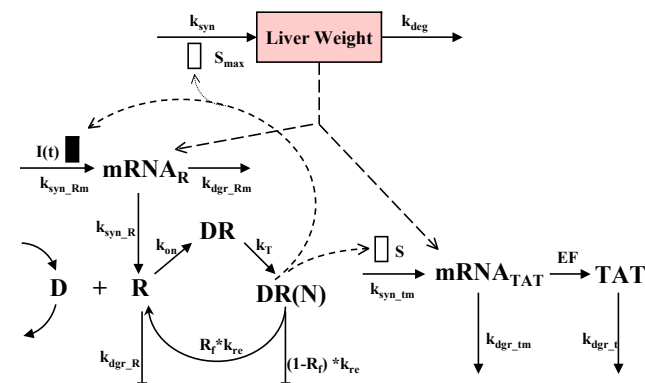


R. Ramakrishnan, DC Debois, RR Almon, NA Pyszczynski, and WJ Jusko, *J. Pharmacokin. Pharmacodyn.* 21: 1-24 (2002).

## Methylprednisolone PK/PD/PG in Rats



## Model for Gene-Mediated Corticosteroid Pharmacodynamics



GENE EXPRESSION MONITORING

**GeneChip®  
Rat Genome U34 Set**


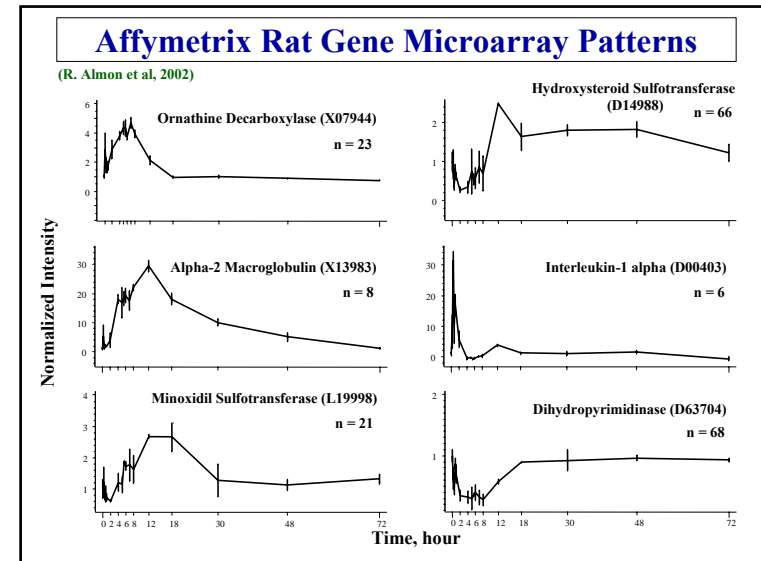
AFFYMETRIX

**Rat Genome Expression Analysis**

- The Rat Genome U34 Set provides gene expression data for >24,000 known genes and EST clusters; the most comprehensive rat genome coverage available.

**Applications**

- The Rat Genome U34 Set is a powerful tool for toxicology, neurobiology,

## Summary

- **Transduction processes control or contribute to many drug responses in converting receptor or mediator signals into pharmacologic responses.**
- **Concepts for rapid, nonlinear transduction and multi-step linear time-dependent transduction have been shown.**
- **It is necessary to measure the intermediary steps or processes in order to develop mechanistic models (eg: pharmacogenomics of corticosteroids).**
- **Modeling transduction processes is a major frontier in PK/PD modeling with some rudimentary models offering promise for further advances.**

