Pharmacodynamics of Methylprednisolone on *Glucocorticoid Receptor* and *Tyrosine Aminotransferase*

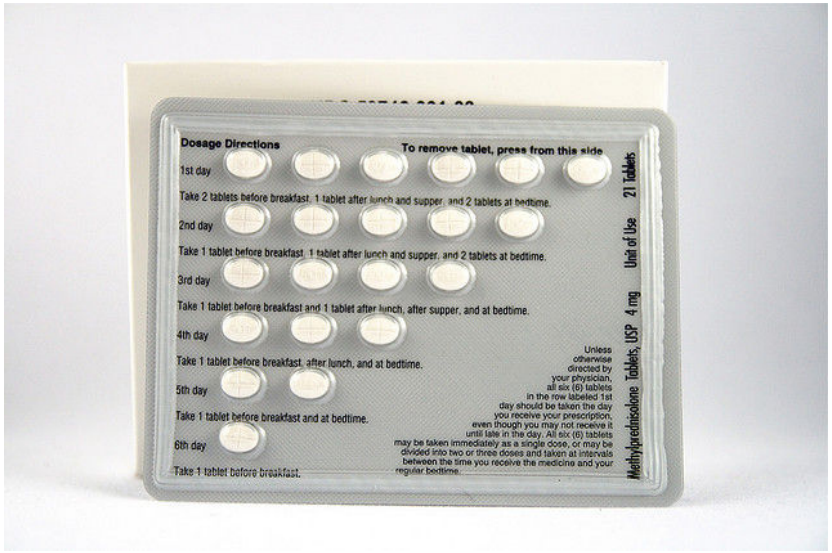
Alexander Vowinkel

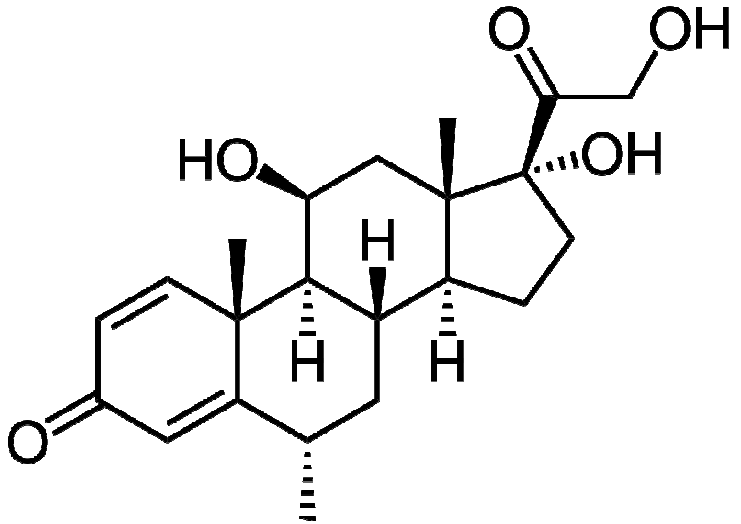
SUN ET AL. *DOSE-DEPENDENCE AND REPEATED-DOSE STUDIES FOR RECEPTOR/GENE-MEDIATED PHARMACODYNAMICS OF METHYLPREDNISOLONE ON GLUCOCORTICOID RECEPTOR DOWN-REGULATION AND TYROSINE AMINOTRANSFERASE INDUCTION IN RAT LIVER*. JOURNAL OF PHARMACOKINETICS AND BIOPHARMACEUTICS, VOL. 26, NO. 6, 1998

Methylprednisolone (MPL)

Systematic name: (1*S*,2*R*,8*S*,10*S*,11*S*,14*R*,15*S*,17*S*)-14,17-dihydroxy-14-(2-hydroxyacetyl)-2,8,15-trimethyltetracyclo[8.7.0.0^{2,7}.0^{11,15}] heptadeca-3,6-dien-5-one

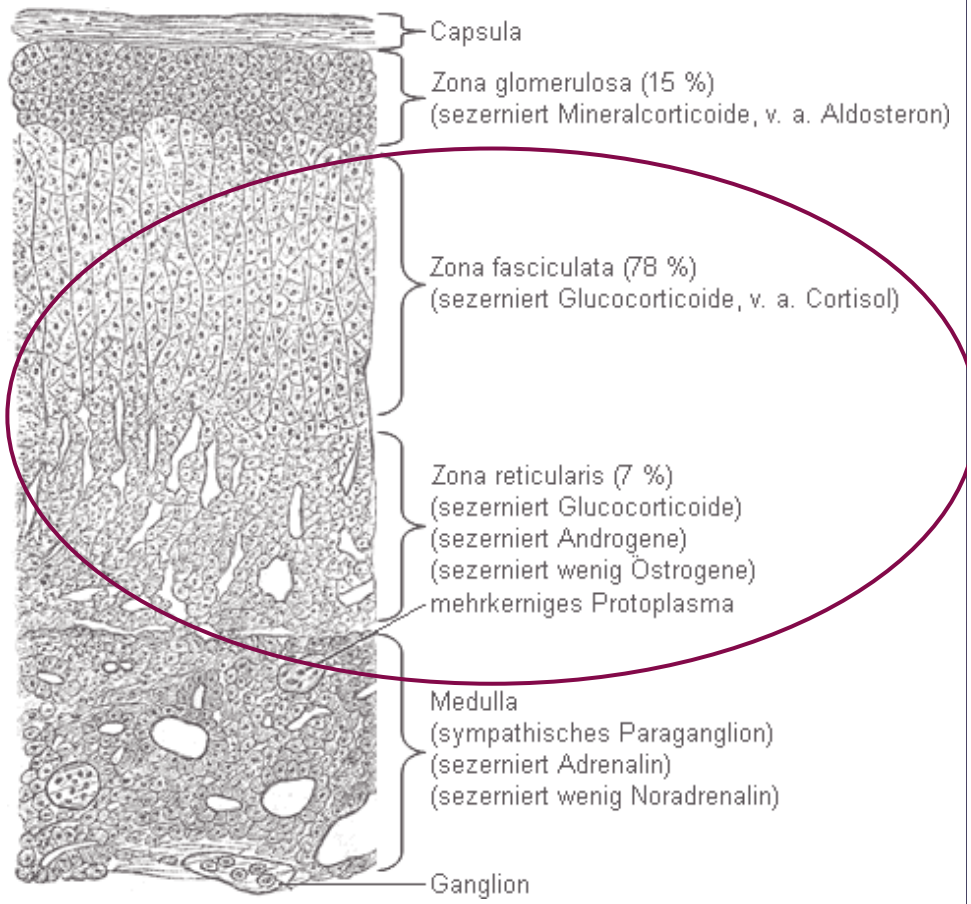
Class: synthetic **glucocorticoid**





Glucocorticoids

- corticosteroid
- produced in adrenal cortex
- inactivation in liver

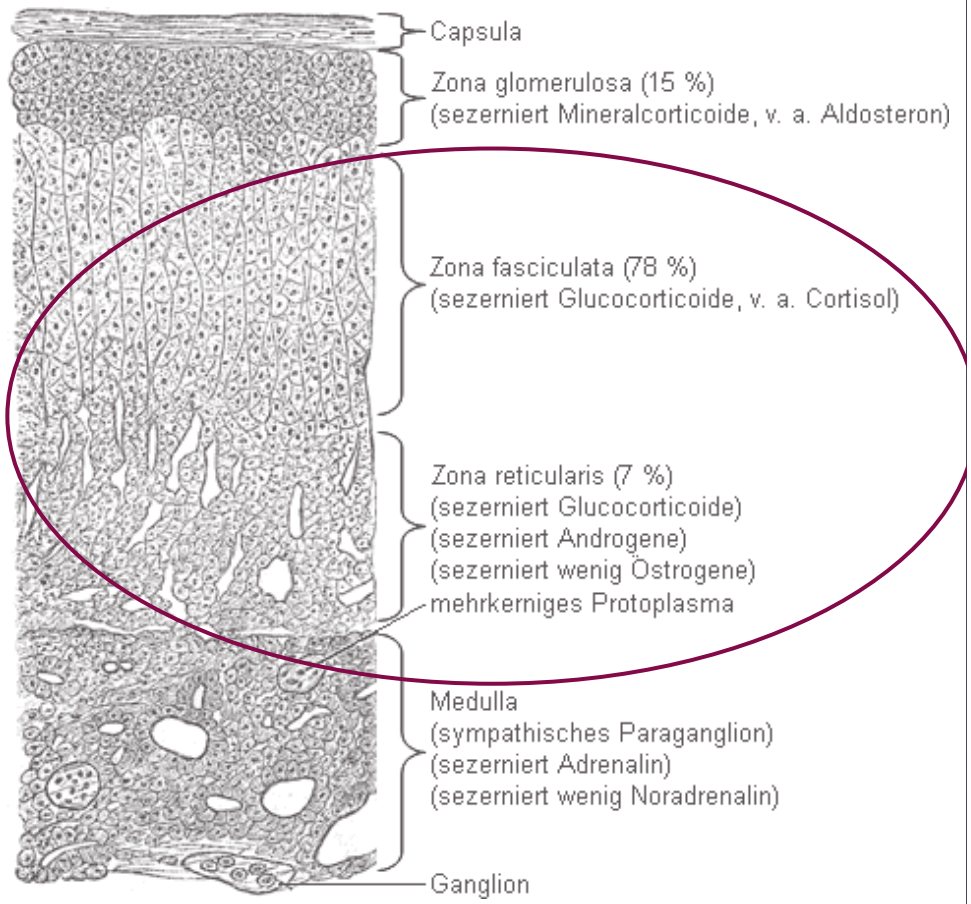


Glucocorticoids

- corticosteroid
- produced in adrenal cortex
- inactivation in liver

- excites gluconeogenesis
  from fat and proteins

=> high blood concentration of
glucose, amino acids,
fatty acids



Methylprednisolone

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Class: synthetic **glucocorticoid**

Desired effects:
- anti-inflammatory
- metabolism
- immune responses

Side effects:

hyperglycemia (high blood sugar)	glaucoma
weight gain	osteoporosis
decreased resistance to infection	psychosis
swelling of face	osteoporosis
cardiac insufficiency	increased eye pressure
fluid and sodium retention	fatal chicken pox viral course
hypertension (high blood pressure)	edema

Methylprednisolone

Systematic name: (1*S*,2*R*,8*S*,10*S*,11*S*,14*R*,15*S*,17*S*)-14,17-dihydroxy-14-(2-hydroxyacetyl)-2,8,15-trimethyltetracyclo[8.7.0.0^{2,7}.0^{11,15}]heptadeca-3,6-dien-5-one

Class: synthetic **glucocorticoid**

Desired effects:

Applications:
- allergic and autoimmune reactions
- skin deseases
- anaphylactic shock / asthma
- cerebral edema
- spinal chord injuries (in USA)

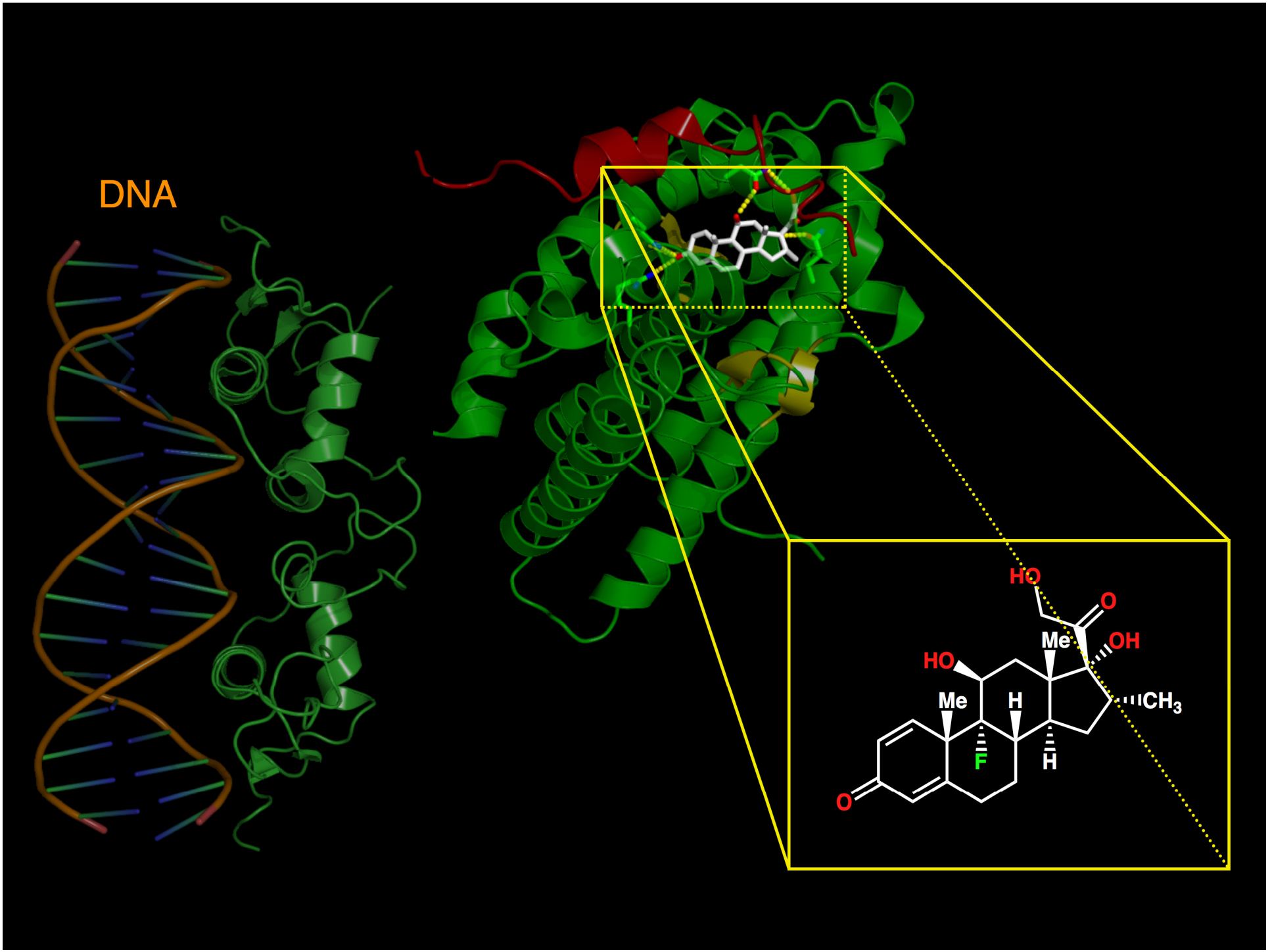
Side effects:

aucoma
teoporosis
decreased resistance to infection
psychosis
swelling of face
osteoporosis
cardiac insufficiency
increased eye pressure
fluid and sodium retention
fatal chicken pox viral course
hypertension (high blood pressure)
edema

Glucocorticoid Receptor (GR)

- regulates genes controlling the development, metabolism, and immune response

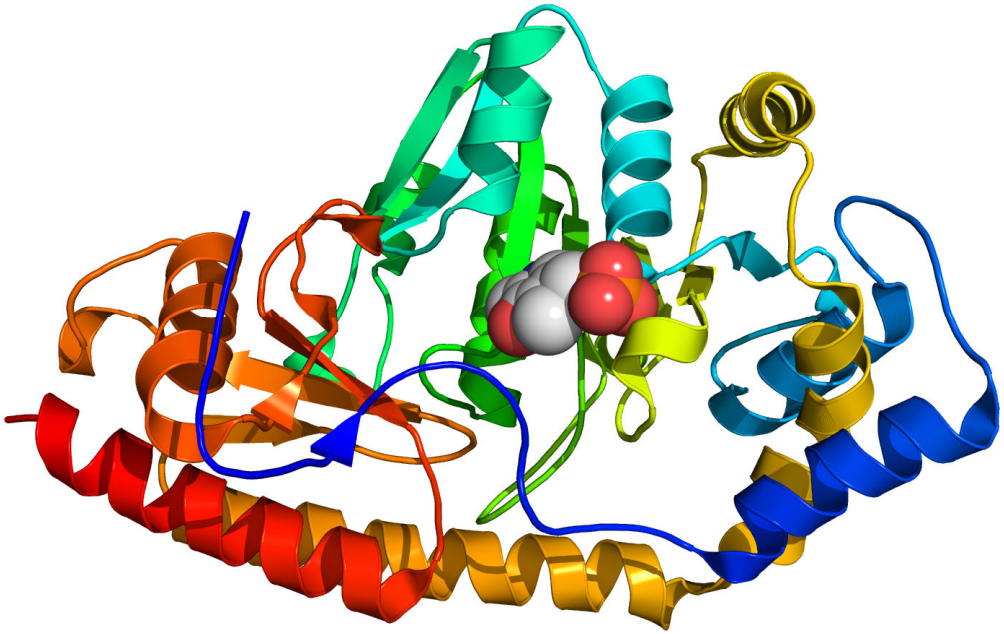
- receptor to which glucocorticoids bind


DNA
HO
O
Me
OH
HO
Me
H
CH3
F
H
O

Tyrosine aminotransferase (TAT)

- plays a role in amino acid metabolism (tyrosine) in liver

- is regulated by activated GR



The study

1. intravenous doses of **MPL** into **rats**
   - 10 mg/kg, 50 mg/kg
2. measurement of **concentrations**
   - mRNA + protein of **GR**
   - mRNA + protein of **TAT**
3. fitting two different models
4. publishing

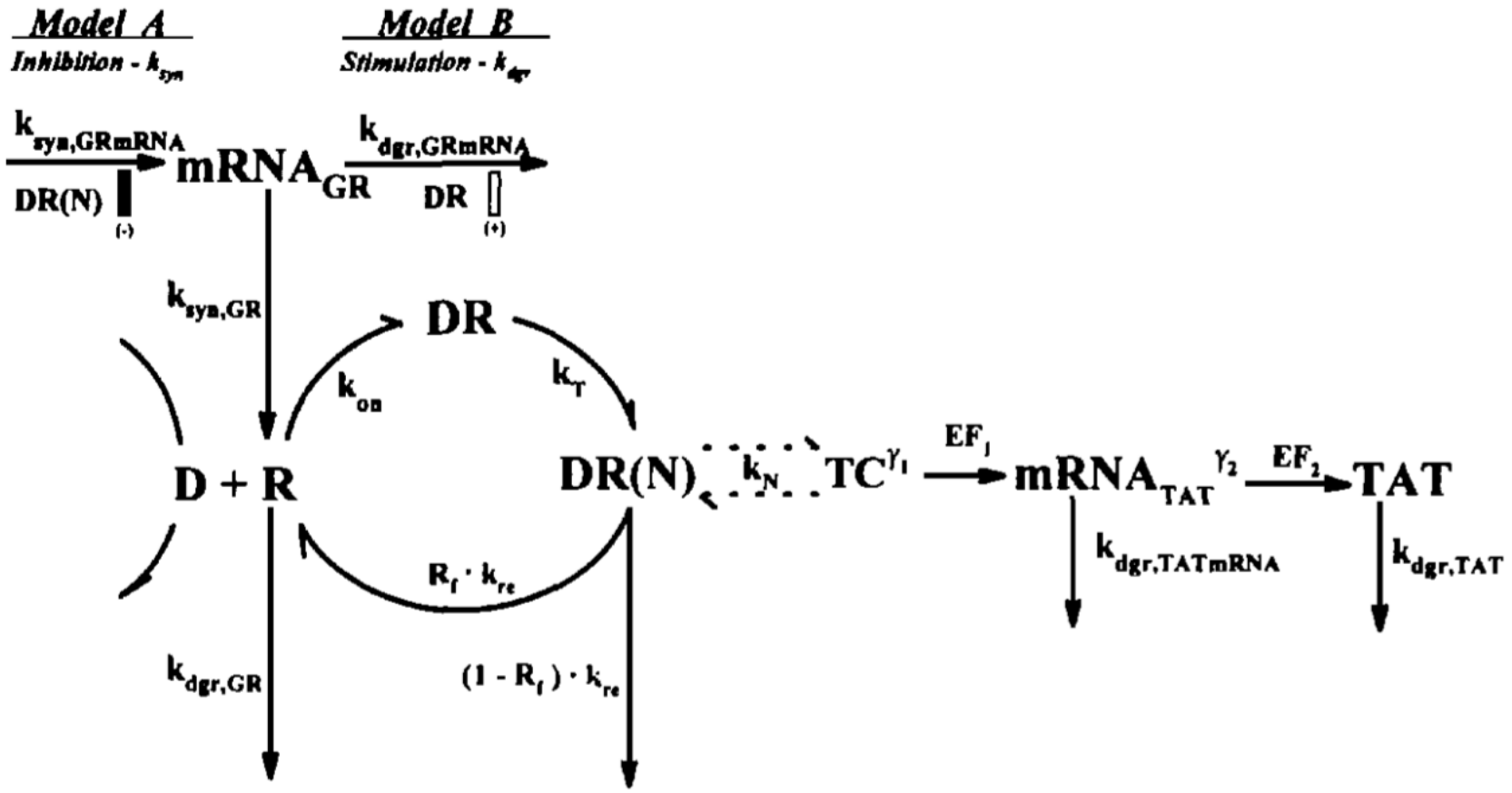
The study

Table II. Pharmacodynamic Parameters Estimated by the Maximum Likelihood Method

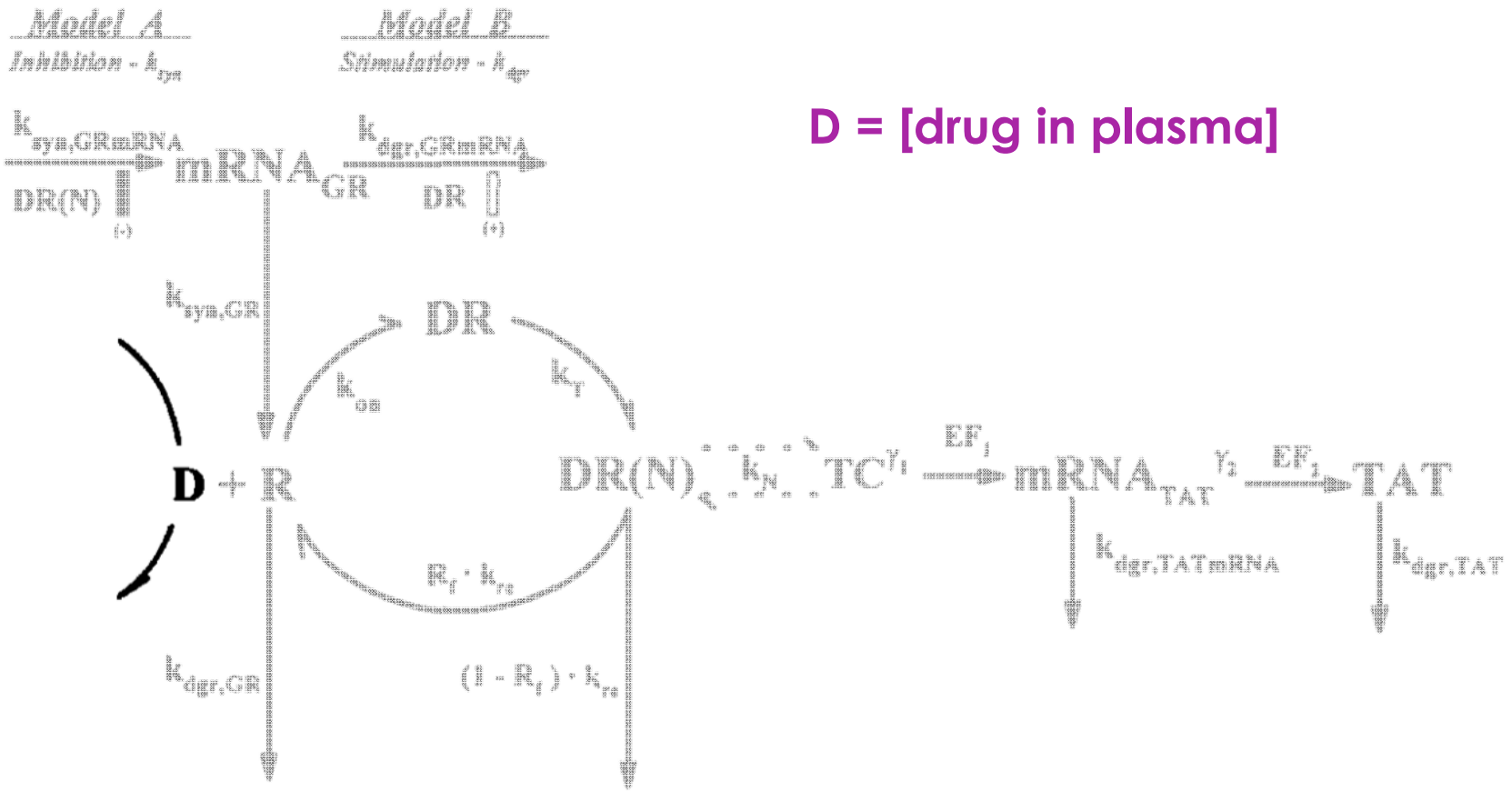
Parameters (units)	Model A (*CV*%)	Model B (*CV*%)
$IC_{50,GRmRNA}$ (nmole/L per mg protein)	50.7 (63)	—[c]
$S_{max,GRmRNA}$	—[c]	2.1 (42)
$SC_{50,GRmRNA}$ (nmole/L per mg protein)	—[c]	36.9 (85)
$k_{syn,GRmRNA}$ (fmole/g per hr)	1.90[a]/1.77[b]	1.03[a]/0.96[b]
$k_{dgr,GRmRNA}$ (hr^{-1})	0.11 (35)	0.06 (41)
k_{on} (L/nmole per hr)	$4.87 \cdot 10^{-4}$ (25)	$4.04 \cdot 10^{-4}$ (13)
$k_{syn,GR}$ (nmole GR/L per mg protein per fmole GR mRNA/g per hr)	1 52[a]/2.10[b]	3.05[a]/4.19[b]
$k_{dgr,GR}$ (hr^{-1})	0.07 (17)	0.14 (38)
R_f	0.46 (23)	0.24 (63)
k_T (hr^{-1})	2.03 (63)	0.39 (43)
k_{re} (hr^{-1})	0.36 (21)	0.37 (37)
k_N (hr^{-1})	0.50 (17)	1.41 (33)
$mRNA_{TAT,0}$ (pmole/g)	0.11[a]/0.07[b] (9,7)	0.11[a]/0.07[b] (9,7)
EF_1 (pmole TAT mRNA/g per nmole GR per mg protein)	$1.58 \cdot 10^{-5}$ (37)	$1.52 \cdot 10^{-5}$ (135)
$k_{dgr,TATmRNA}$ (hr^{-1})	1.3 (32)	1.7 (43)
γ_1	1.9 (15)	2.0 (13)
TAT_0 (ΔA/mg protein)	0.07 (11[a]/7[b])	0.07 (7[a]/8[b])
EF_2 (ΔA/mg of protein per pmole of TAT mRNA/g)	2.21 (17)	2.87 (21)
$k_{dgr,TAT}$ (hr^{-1})	0.99 (16)	1.41 (20)
γ_2	0.82 (9)	0.79 (9)

[a] Results for 10 mg/kg MPL.
[b] Results for 50 mg/kg MPL.
[c] Not applicable.

Two Models

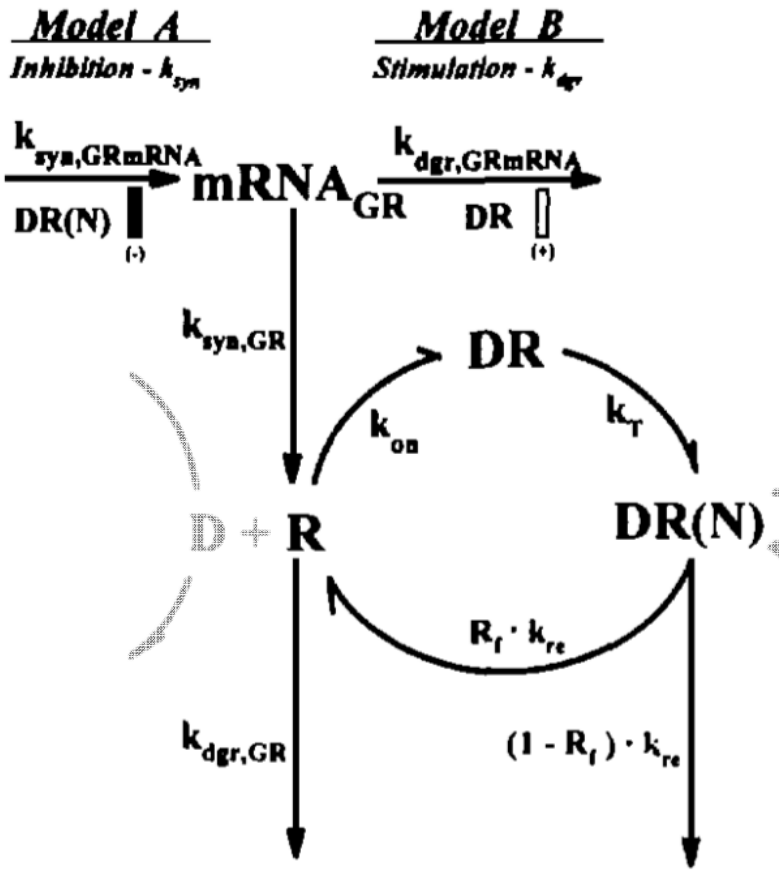

Model A
Inhibition - k_{syn}
Model B
Stimulation - k_{dgr}
$k_{syn,GRmRNA}$
DR(N)
(-)
$mRNA_{GR}$
$k_{dgr,GRmRNA}$
DR
(+)
$k_{syn,GR}$
DR
k_{on}
k_T
D + R
DR(N)
k_N
TC^{γ_1}
EF_1
$mRNA_{TAT}$
γ_2
EF_2
TAT
$k_{dgr,TATmRNA}$
$k_{dgr,TAT}$
$R_f \cdot k_{re}$
$k_{dgr,GR}$
$(1 - R_f) \cdot k_{re}$

Part 0 - Parmacokinetics



D = [drug in plasma]

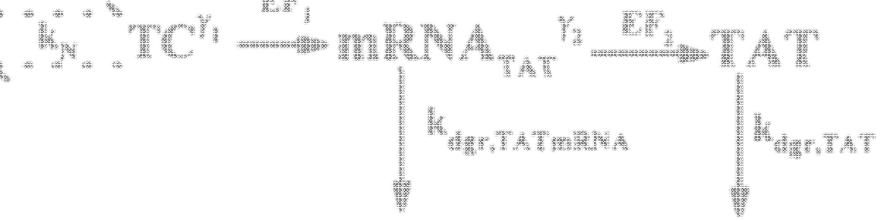
Part 1 - GR cycle



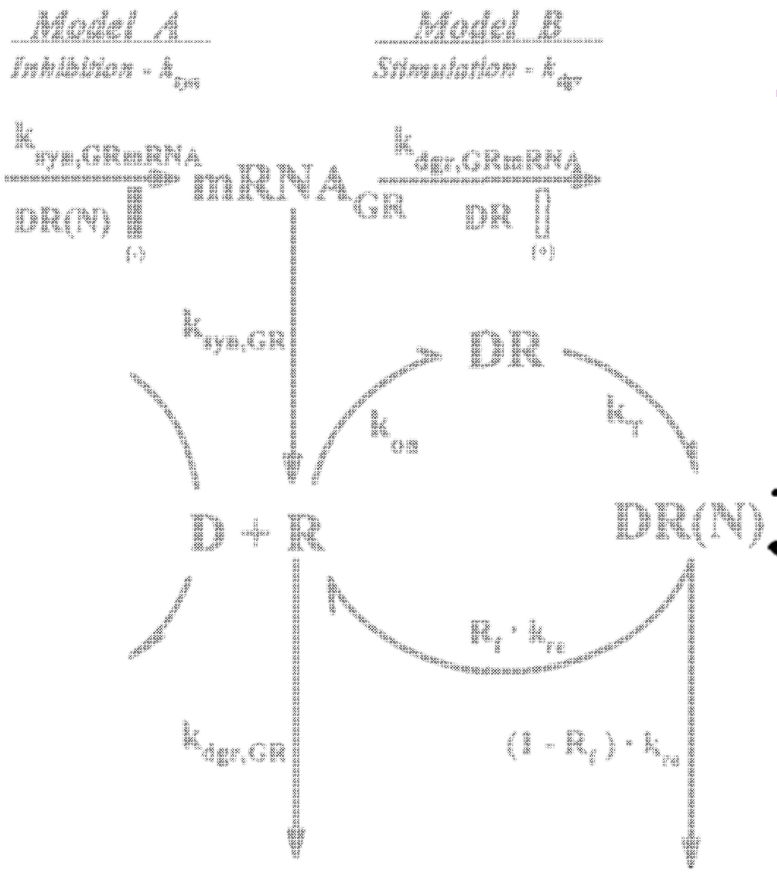
R = receptor protein

DR = drug bonded on receptor

DR(N) = DR in nucleus

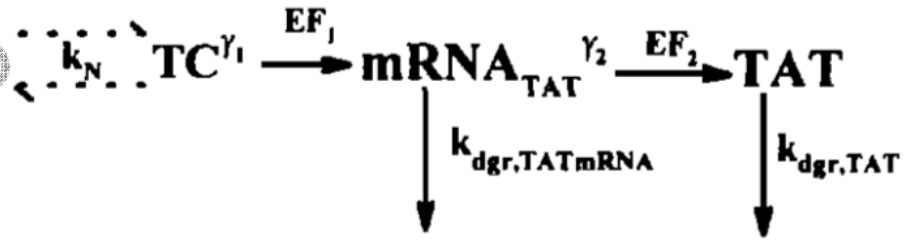


Part 2 - TAT cycle

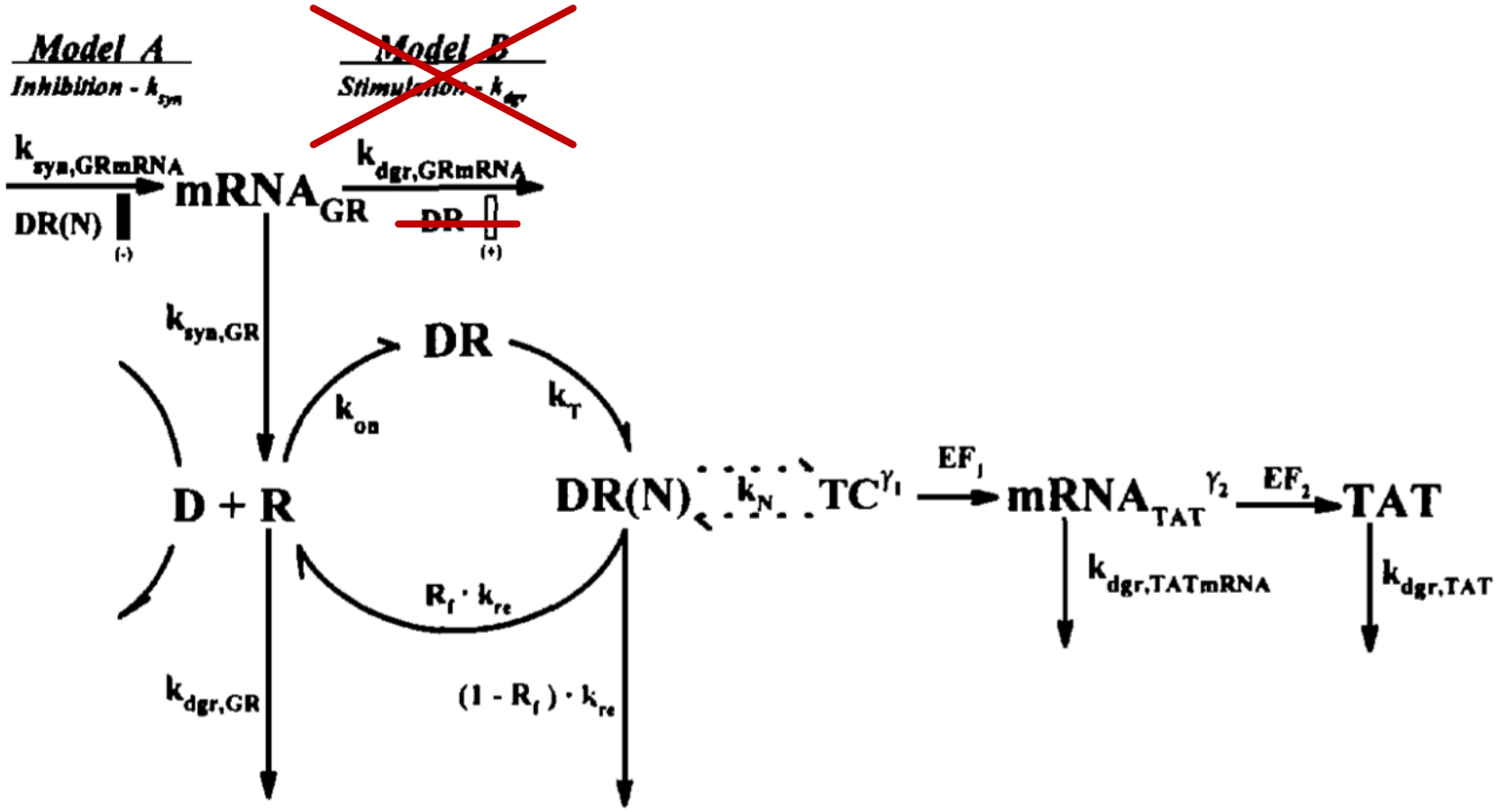


TC = transcription compartment

EF = transcription factor



Two Models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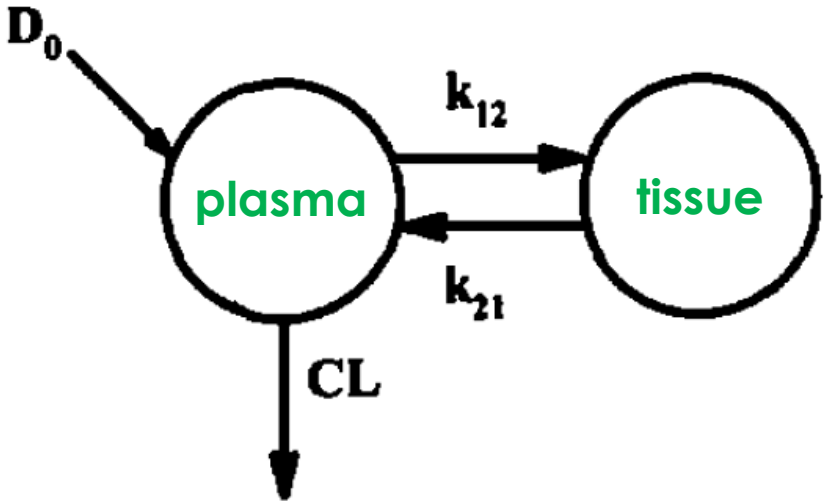
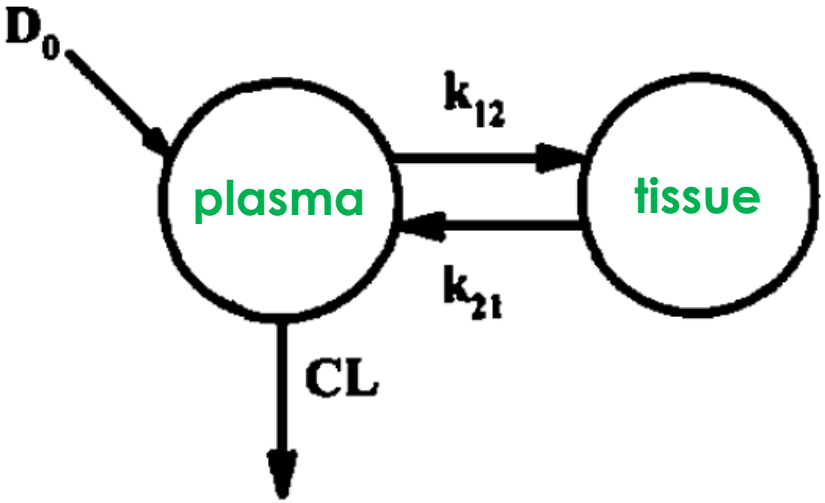
Inhibition - k_{syn}
Model B
Stimulation - k_{dgr}
$k_{syn,GRmRNA}$
DR(N)
(-)
$mRNA_{GR}$
$k_{dgr,GRmRNA}$
DR
(+)
$k_{syn,GR}$
DR
k_{on}
k_T
D + R
DR(N)
k_N
TC^{γ_1}
EF_1
$mRNA_{TAT}$
γ_2
EF_2
TAT
$k_{dgr,TATmRNA}$
$k_{dgr,TAT}$
$R_f \cdot k_{re}$
$k_{dgr,GR}$
$(1 - R_f) \cdot k_{re}$

Pharmacokinetics (descriptive)



- D_0: intravenous drug administration
- CL: Clearance
- k_{12}, k_{21}: volume diffusion parameter

Pharmacokinetics (descriptive)



$$\frac{dA_p}{dt} = -(CL/V_c) \cdot A_p - k_{12} \cdot A_p + k_{21} \cdot A_t$$

$$\frac{dA_t}{dt} = k_{12} \cdot A_p - k_{21} \cdot A_t$$

Pharmacokinetics (descriptive)

reminder - ∀species i:

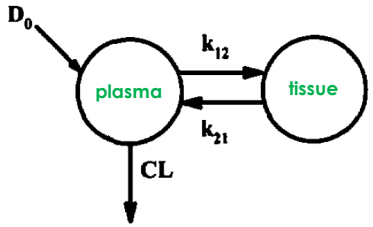
$$\frac{d}{dt}X_i = \sum_j s_{i,j} \cdot r_j(X,p)$$

$$\frac{d}{dt}X = S \cdot R(X,p)$$

(1)

$$\frac{dA_p}{dt} = -(CL/V_c) \cdot A_p - k_{12} \cdot A_p + k_{21} \cdot A_t$$

$$\frac{dA_t}{dt} = k_{12} \cdot A_p - k_{21} \cdot A_t$$

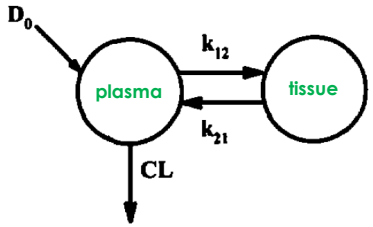


Pharmacokinetics (descriptive)

$$\frac{d}{dt}X = S \cdot \boldsymbol{R(X,p)}$$

$$\frac{dA_p}{dt} = \overset{(1)}{-(CL/V_c)\cdot A_p} \overset{(2)}{-k_{12}\cdot A_p} \overset{(3)}{+k_{21}\cdot A_t}$$

$$\frac{dA_t}{dt} = \overset{(2)}{k_{12}\cdot A_p} \overset{(3)}{-k_{21}\cdot A_t}$$

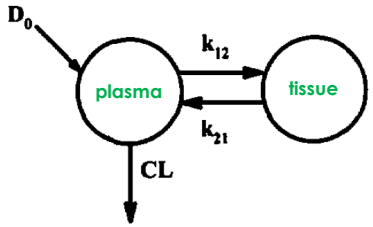


Pharmacokinetics (descriptive)

$$\frac{d}{dt}X = \boldsymbol{S} \cdot R(X,p)$$

$$\frac{dA_p}{dt} = -(CL/V_c) \cdot A_p - k_{12} \cdot A_p + k_{21} \cdot A_t$$

$$\frac{dA_t}{dt} = k_{12} \cdot A_p - k_{21} \cdot A_t$$



Pharmacokinetics (descriptive)

$$\frac{d}{dt}X = S \cdot R(X,p)$$

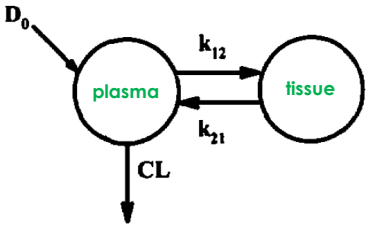
$$S = \begin{pmatrix} \overset{(1)}{-1} & \overset{(2)}{-1} & \overset{(3)}{+1} \\ 0 & +1 & -1 \end{pmatrix}$$

$$\frac{dA_p}{dt} = -(CL/V_c)\cdot A_p - k_{12}\cdot A_p + k_{21}\cdot A_t$$

(1) (2) (3)

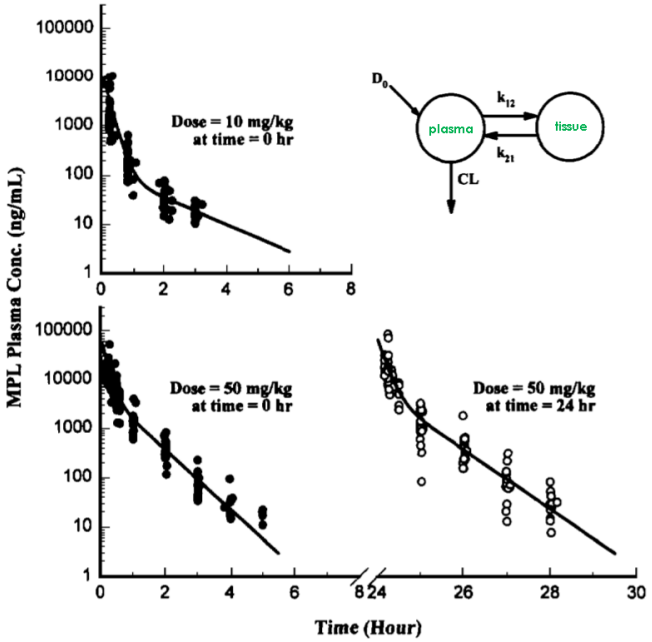
$$\frac{dA_t}{dt} = k_{12}\cdot A_p - k_{21}\cdot A_t$$

(2) (3)

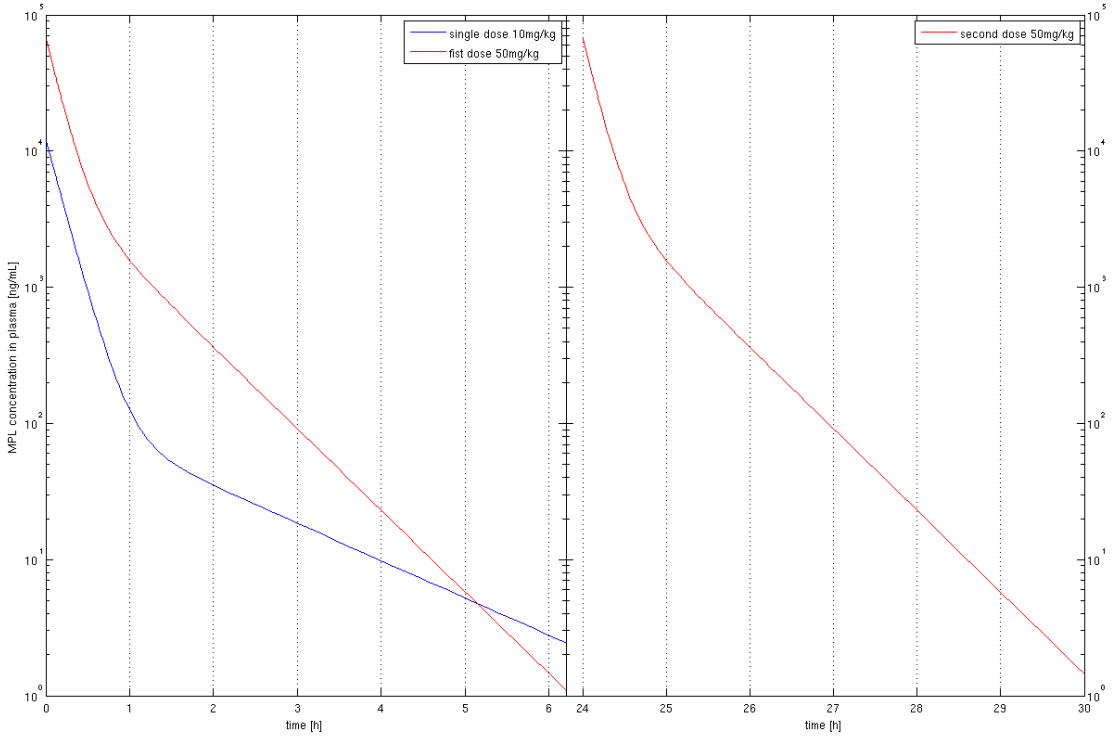


Results / Comparison

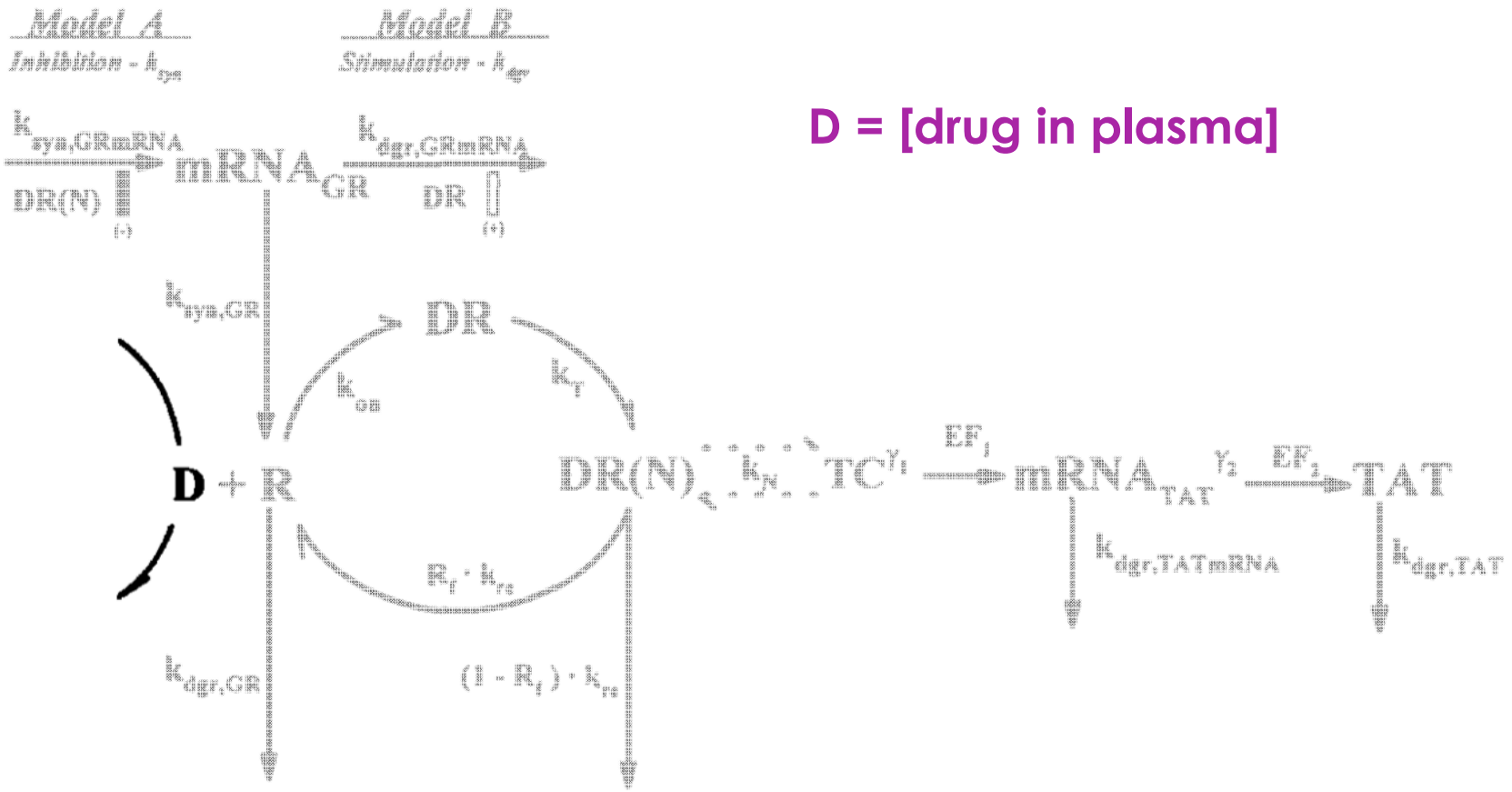
paper



reproduction

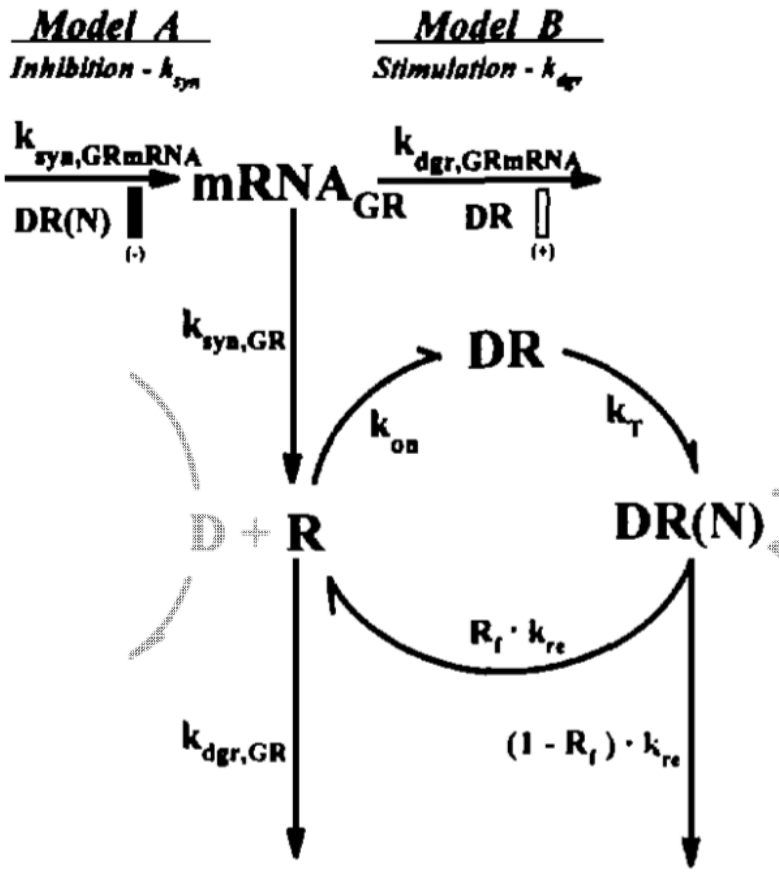


Part 0 - Parmacokinetics



D = [drug in plasma]

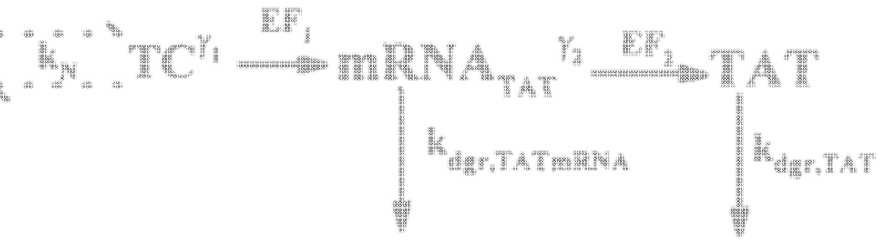
Part 1 - GR cycle



R = receptor protein

DR = drug bonded on receptor

DR(N) = DR in nucleus



Part 1 - GR cycle

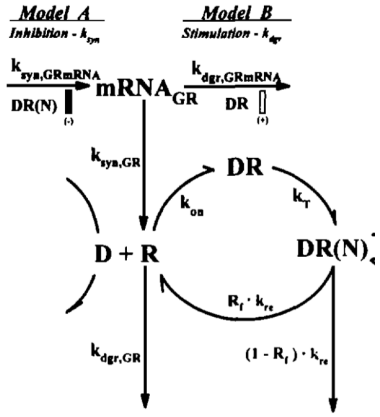
$$\begin{pmatrix} +1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & +1 & +1 & -1 & 0 & 0 \\ 0 & 0 & +1 & 0 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & +1 & -1 \end{pmatrix}$$

$$\frac{dmRNA_{GR}}{dt} = k_{syn,GRmRNA} \cdot \left(1 - \frac{DR(N)}{IC_{50,GRmRNA} + DR(N)}\right) - k_{dgr,GRmRNA} \cdot mRNA_{GR}$$

$$\frac{dR}{dt} = -k_{on} \cdot D \cdot R + k_{syn,GR} \cdot mRNA_{GR} + (R_f \cdot k_{re}) \cdot DR(N) - k_{dgr,GR} \cdot R$$

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

$$\frac{dDR(N)}{dt} = k_T \cdot DR - k_{re} \cdot DR(N)$$



Part 1 - GR cycle

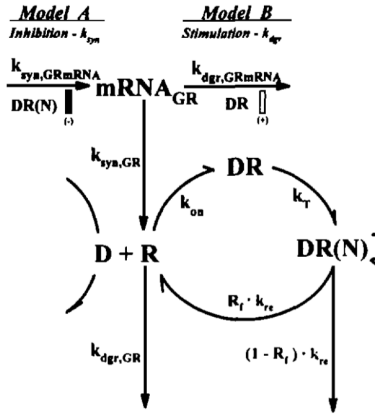
$$\left(\begin{array}{cc|cccc|cc} +1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & +1 & +1 & -1 & 0 & 0 \\ \hline 0 & 0 & +1 & 0 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & +1 & -1 \end{array}\right)$$

$$\frac{dmRNA_{GR}}{dt} = k_{syn,GRmRNA} \cdot \left(1 - \frac{DR(N)}{IC_{50,GRmRNA} + DR(N)}\right) - k_{dgr,GRmRNA} \cdot mRNA_{GR}$$

$$\frac{dR}{dt} = -k_{on} \cdot D \cdot R + k_{syn,GR} \cdot mRNA_{GR} + (R_f \cdot k_{re}) \cdot DR(N) - k_{dgr,GR} \cdot R$$

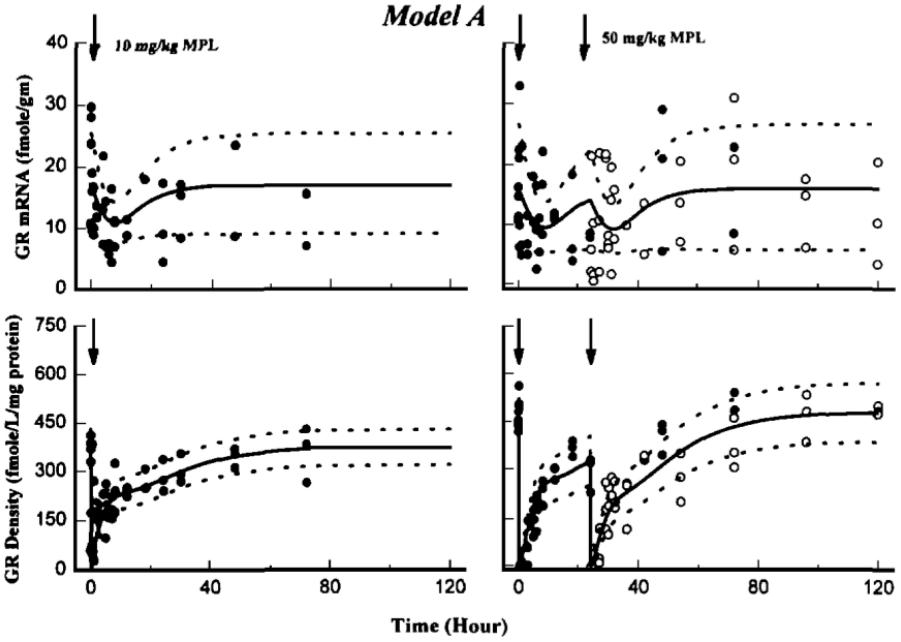
$$\frac{dDR}{dt} = k_{on} \cdot D \cdot R - k_T \cdot DR$$

$$\frac{dDR(N)}{dt} = k_T \cdot DR - k_{re} \cdot DR(N)$$

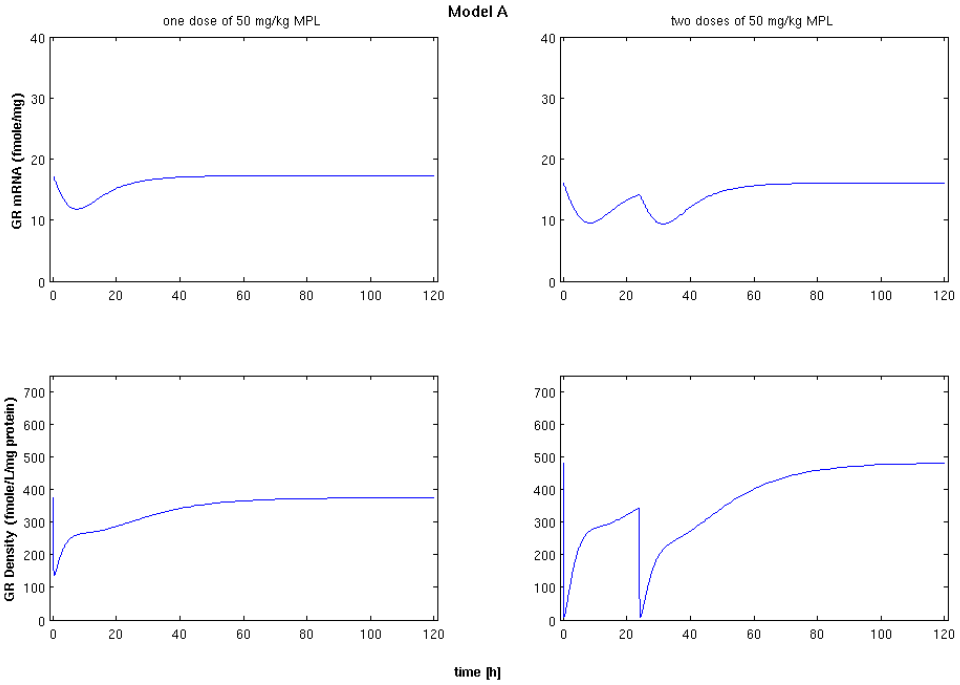


Results / Comparison

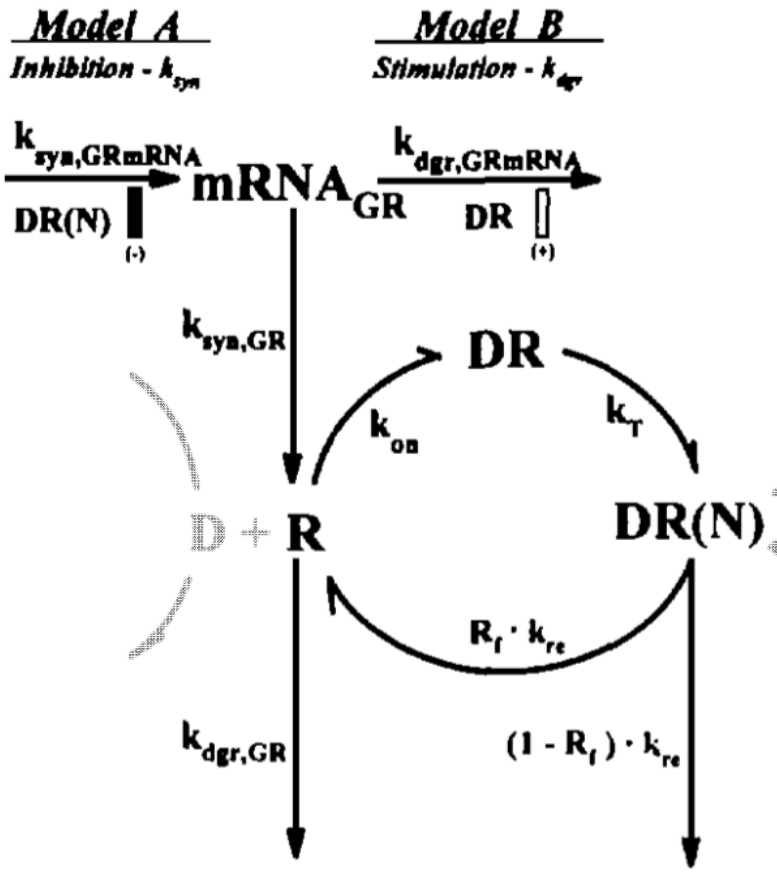
paper



reproduction



Part 1 - GR cycle



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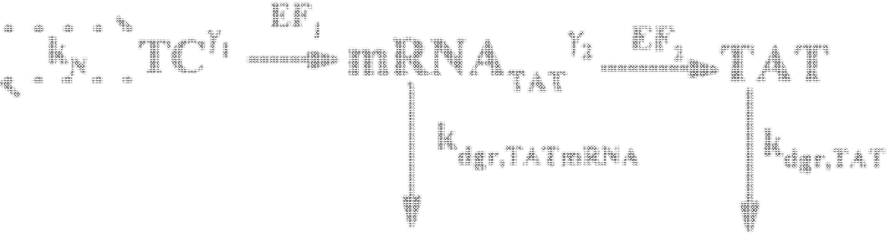
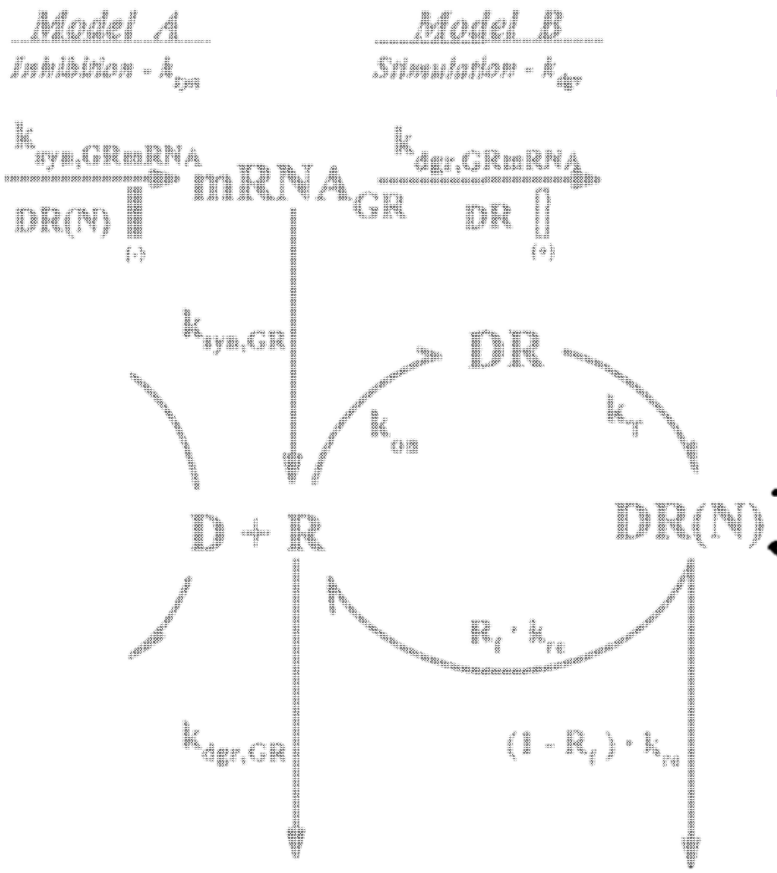


Part 2 - TAT cycle



TC = transcription compartment

EF = transcription factor

Part 1 - GR cycle

$$\frac{dTC}{dt} = k_N \cdot DR(N) - k_N \cdot TC$$

$$\frac{dmRNA_{TAT}}{dt} = EF_1 \cdot TC^{\gamma_1} - k_{dgr,TATmRNA} \cdot (mRNA_{TAT} - mRNA_{TAT,0})$$

$$\frac{dTAT}{dt} = EF_2 \cdot (mRNA_{TAT} - mRNA_{TAT,0})^{\gamma_2} - k_{dgr,TAT} \cdot (TAT - TAT_0)$$

Part 1 - GR cycle

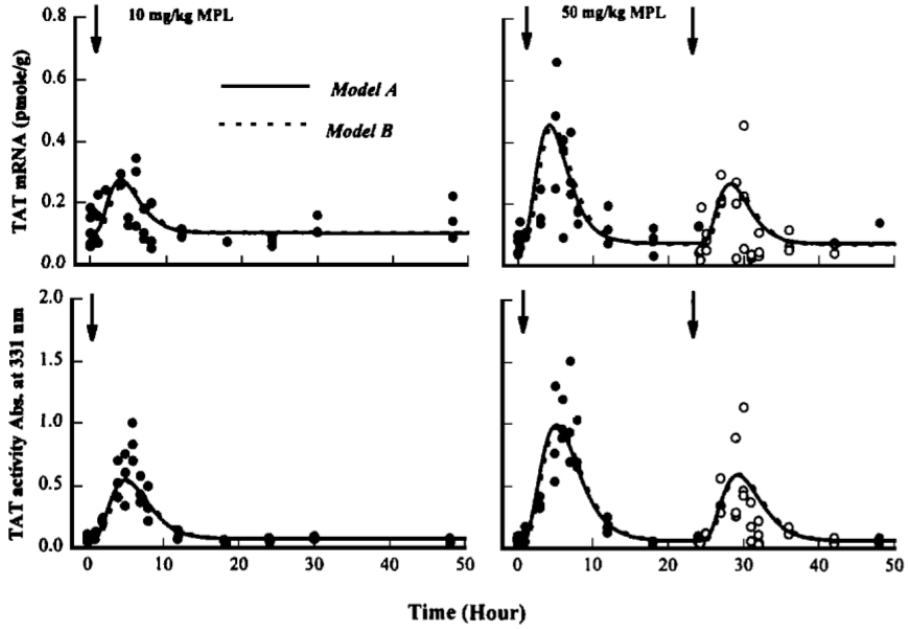
$$\frac{dTC}{dt} = k_N \cdot DR(N) - k_N \cdot TC$$

$$\frac{dmRNA_{TAT}}{dt} = EF_1 \cdot TC^{\gamma_1} - k_{dgr,TATmRNA} \cdot (mRNA_{TAT} - mRNA_{TAT,0})$$

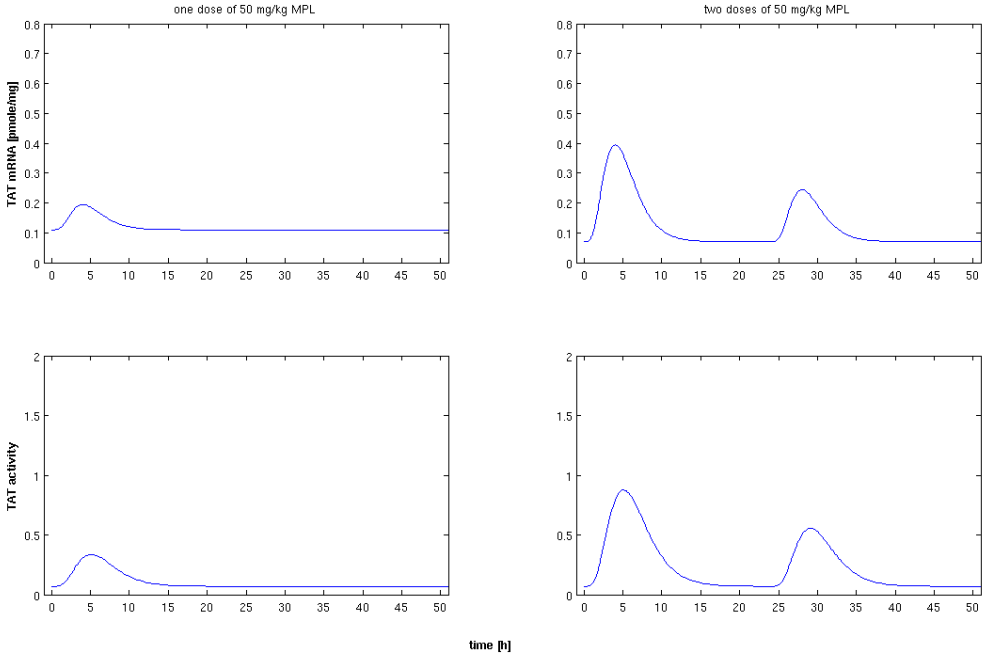
$$\frac{dTAT}{dt} = EF_2 \cdot (mRNA_{TAT} - mRNA_{TAT,0})^{\gamma_2} - k_{dgr,TAT} \cdot (TAT - TAT_0)$$

Results / Comparison

paper



reproduction

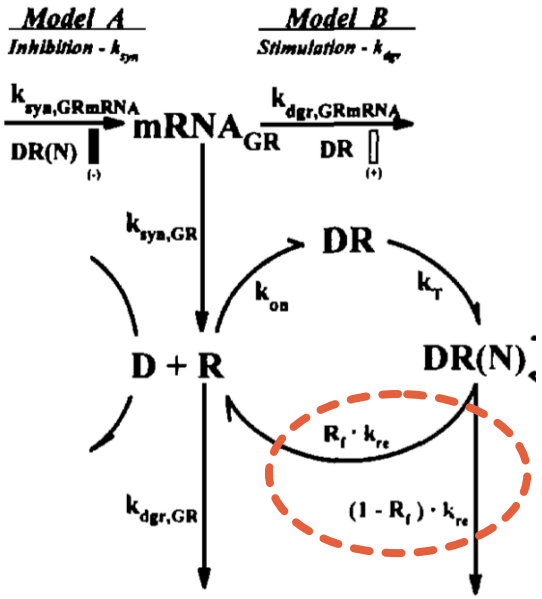


Conclusion

- Model describes the measured data good
- Model gives a description of pharmacodynamics and pharmacokinetics of the pharmacological pathway of methyprednisolon
- Results are reproducable with the model parameters

Conclusion

- Model uses different approaches / is inconsistent / is badly described



$$\frac{dmRNA_{GR}}{dt} = k_{syn,GRmRNA} \cdot \left(1 - \frac{DR(N)}{IC_{50,GRmRNA} + DR(N)}\right) - k_{dgr,GRmRNA} \cdot mRNA_{GR}$$

$$\frac{dR}{dt} = -k_{on} \cdot D \cdot R + k_{syn,GR} \cdot mRNA_{GR} + (R_f \cdot k_{re}) \cdot DR(N) - k_{dgr,GR} \cdot R$$

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

$$\frac{dDR(N)}{dt} = k_T \cdot DR - k_{re} \cdot DR(N)$$

Conclusion

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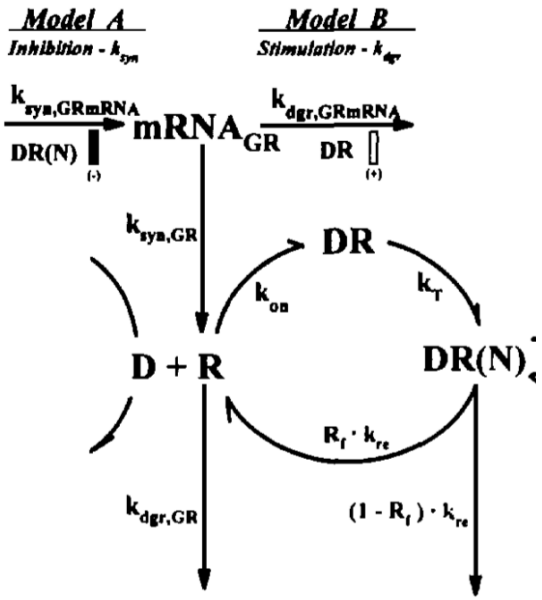

$$\frac{dmRNA_{GR}}{dt} = k_{syn,GRmRNA}\left(1 - \frac{DR(N)}{IC_{50,GRmRNA} + DR(N)}\right) - k_{dgr,GRmRNA} \cdot mRNA_{GR}$$

$$\frac{dR}{dt} = -k_{on} \cdot D \cdot R + k_{syn,GR} \cdot mRNA_{GR} + (R_f \cdot k_{re}) \cdot DR(N) - k_{dgr,GR} \cdot R$$

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

$$\frac{dDR(N)}{dt} = k_T \cdot DR - k_{re} \cdot DR(N)$$

Conclusion

- Model uses different approaches / is inconsistent / is badly described

$$\frac{dR}{dt} = -k_{on} \cdot D \cdot R + k_{syn,GR} \cdot mRNA_{GR} + (R_f \cdot k_{re}) \cdot DR(N) - k_{dgr,GR} \cdot R$$

$$\frac{dTAT}{dt} = EF_2 \cdot (mRNA_{TAT} - mRNA_{TAT,0})^{\gamma_2} + k_{dgr,TAT} \cdot (TAT - TAT_0)$$

Conclusion

- Model uses different approaches / is inconsistent / is badly described

- Model is chosen numerically bad

$$\frac{dTAT}{dt} = EF_2 \cdot (mRNA_{TAT} - mRNA_{TAT,0})^{\gamma_2} \qquad 0.82$$

Conclusion

- Model uses different approaches / is inconsistent / is badly described
- Model is chosen numerically bad
- Units are a mess

$k_{syn,GR}$ (nmole GR/L per mg protein per fmole GR mRNA/g per hr)

TAT_0 (ΔA/mg protein)

Conclusion

- Model uses different approaches / is inconsistent / is badly described
- Model is chosen numerically bad
- Units are a mess
- Different parameter for different doses

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- Different parameter for different doses

FIN

THANK YOU FOR THE FISH

Implementation in Matlab

```
function [T, Y] = myMPLDosing_single(y0, p, duration)
    % initiale Parameter festlegen
    weight = 0.213; % subject weight
    Tspan = [ 0 duration ]; % [min]

    RTol = 1e-4; % relative tolerance
    ATol = 1e-6; % absolute tolerance
    options = odeset('RelTol', RTol, 'AbsTol', ATol, 'NonNegative', [1 2]);

    [T, Y] = ode15s(@(t, y) f(t, y, p), Tspan, y0, options);
end

%% y' = f(t, y, p)
%  A_p' = -CL/V_C * A_p - k_12 * A_p + k_21 * A_t
%  A_t' =                 k_12 * A_p - k_21 * A_t
function y_d = f(~, y, p)
    A_p = y(1); A_t = y(2);
    S = [ -1 -1  1 ; ...
           0  1 -1 ];
    rCoeff = p .* [ A_p A_p A_t ];
    y_d = S * rCoeff';
end
```