St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Modeling Chemotherapy Induced Myelosuppression

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ST. JUDE CHILDREN'S RESEARCH HOSPITAL
1
2
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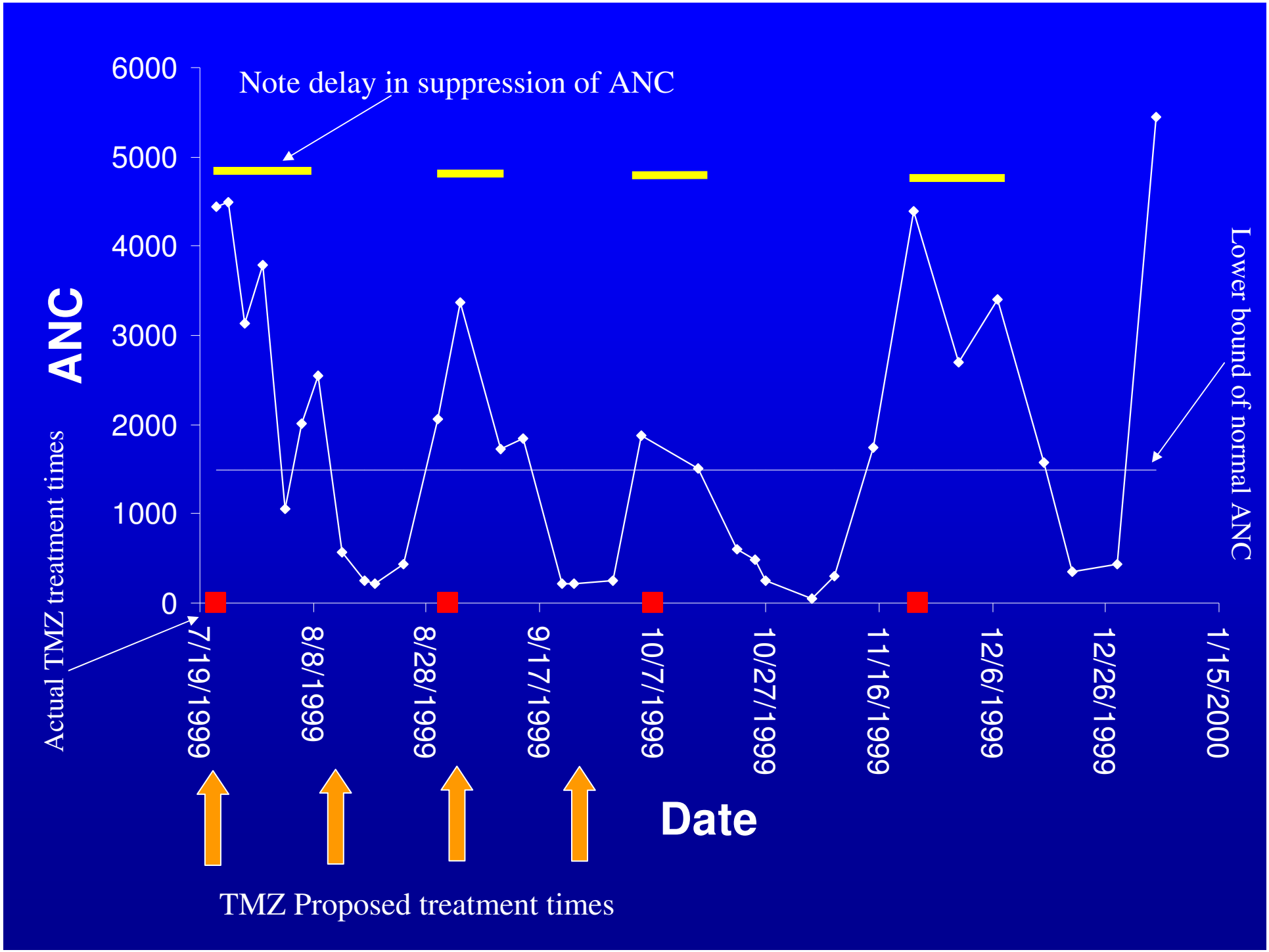
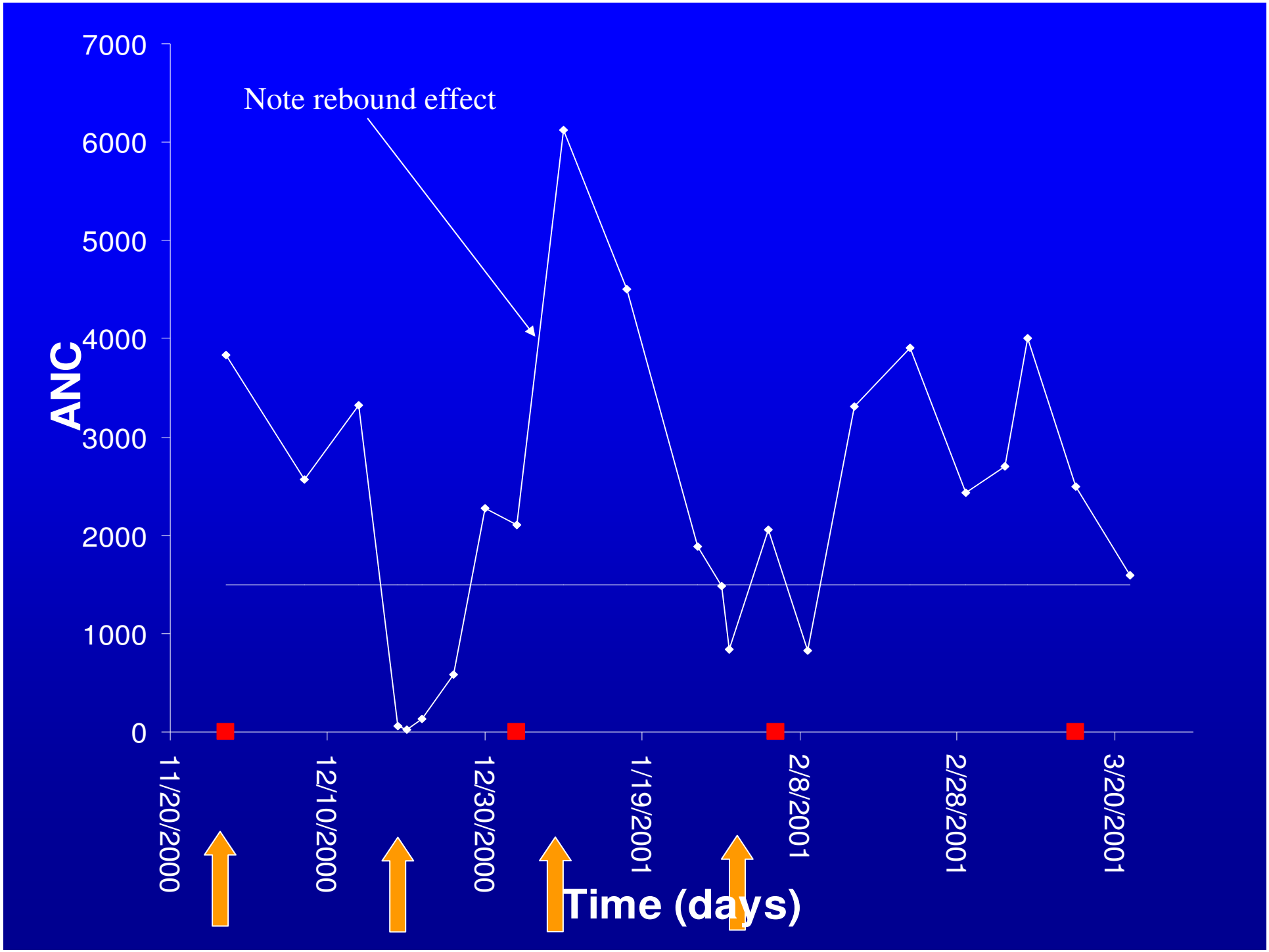
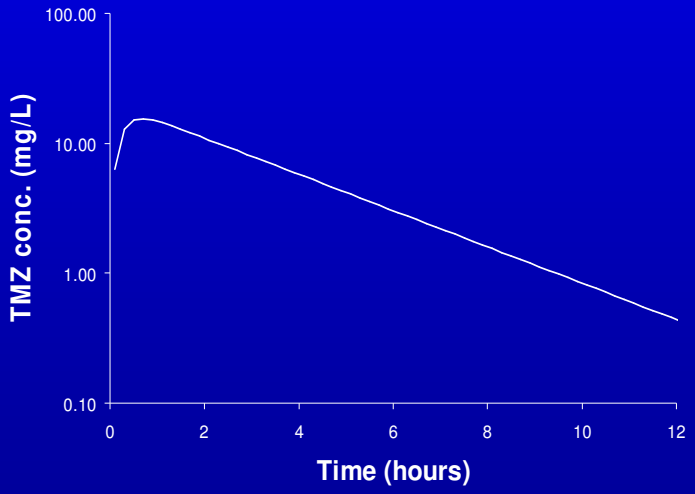
6
7
8
9
10
11
12
13
14
1. Danny Thomas/ALSAC Pavilion
2. Patient Care Center (PCC)
3. ALSAC Tower
4. Danny Thomas Research Tower (DTRT)
5. Integrated Research Center (IRC)
6. St Jude Parking Garage
7. 505 Building/Human Resources/Security
8. Tamer-Rashid Building (ALSAC)
9. Translational Trials Unit (TTU)
10. Barry/Longinotti Building
11. Barry/Longinotti Building Parking Lot
12. ALSAC Parking Lot
13. Good Manufacturing Process Facility
14. Memphis Grizzlies House

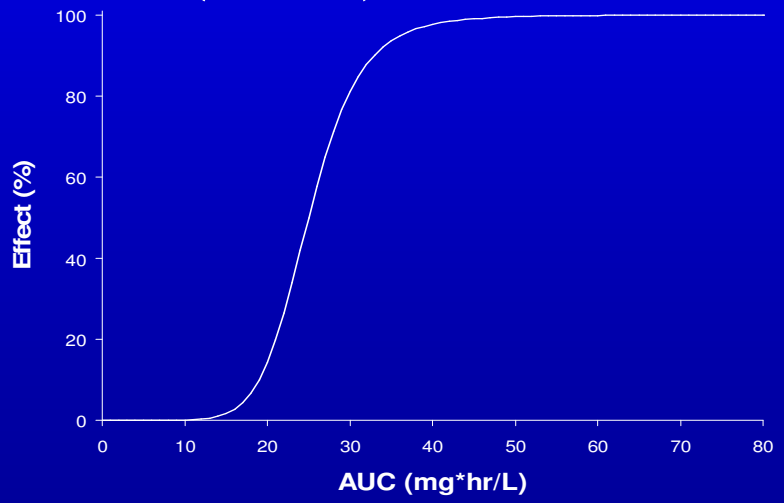

Note delay in suppression of ANC
6000
5000
4000
3000
2000
1000
0
ANC
Lower bound of normal ANC
Actual TMZ treatment times
7/19/1999
8/8/1999
8/28/1999
9/17/1999
10/7/1999
10/27/1999
11/16/1999
12/6/1999
12/26/1999
1/15/2000
Date
TMZ Proposed treatment times


Note rebound effect
ANC
7000
6000
5000
4000
3000
2000
1000
0
11/20/2000
12/10/2000
12/30/2000
1/19/2001
2/8/2001
2/28/2001
3/20/2001
Time (days)

Empirical Modeling Methods

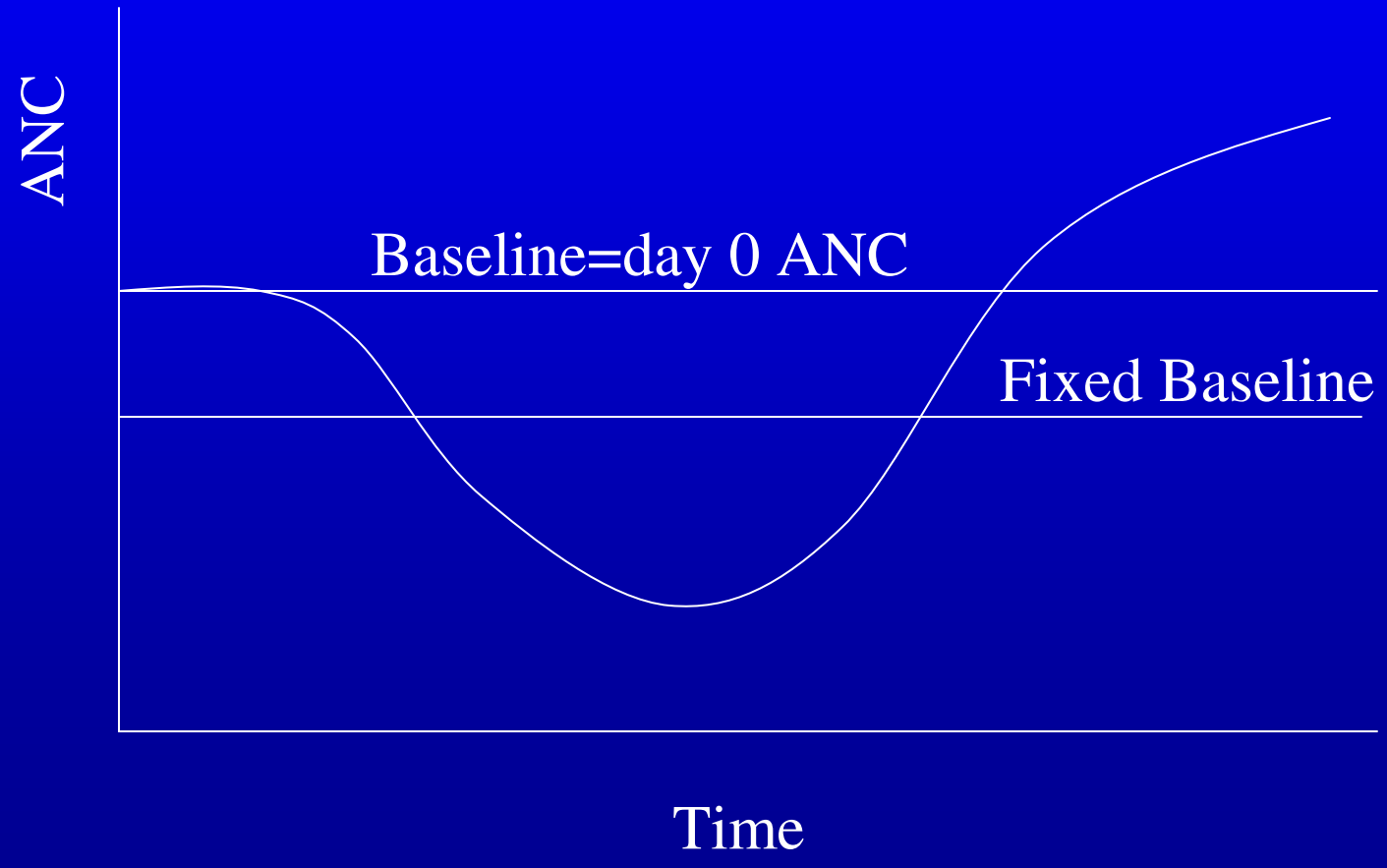
- Describe the Pharmacodynamic (PD) effects of TMZ based on empirical relations between
  - *PK effects*: AUC, time above threshold etc.
  - *PD effects*: Nadir, time between courses, or area between ANC curve (ABC).





- Useful in determining acceptable dose range

Area Between the Curve (ABC)



Karlsson Model

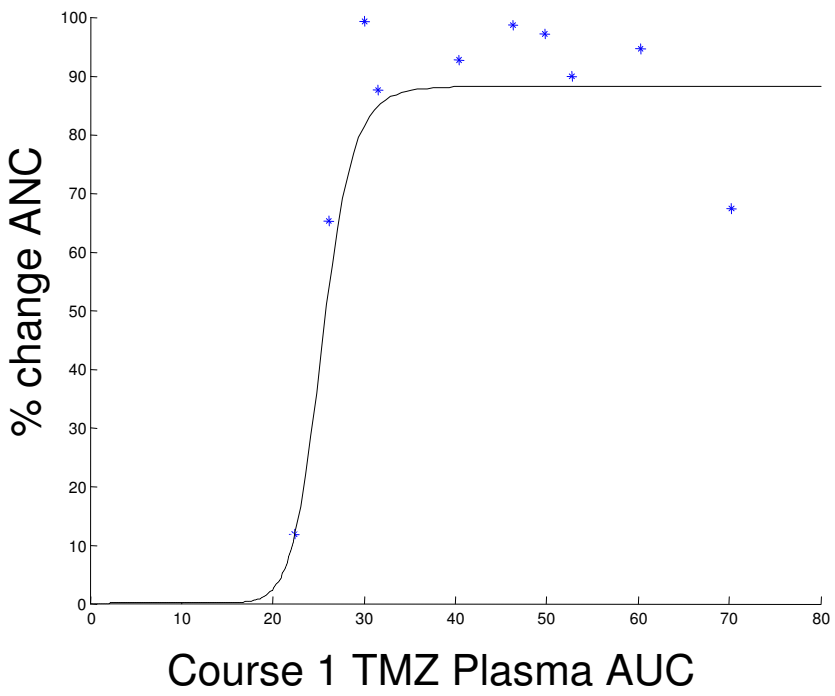
(Karlsson, MO *et al.*, Clin. Pharmacol. Ther. 1998; 63)

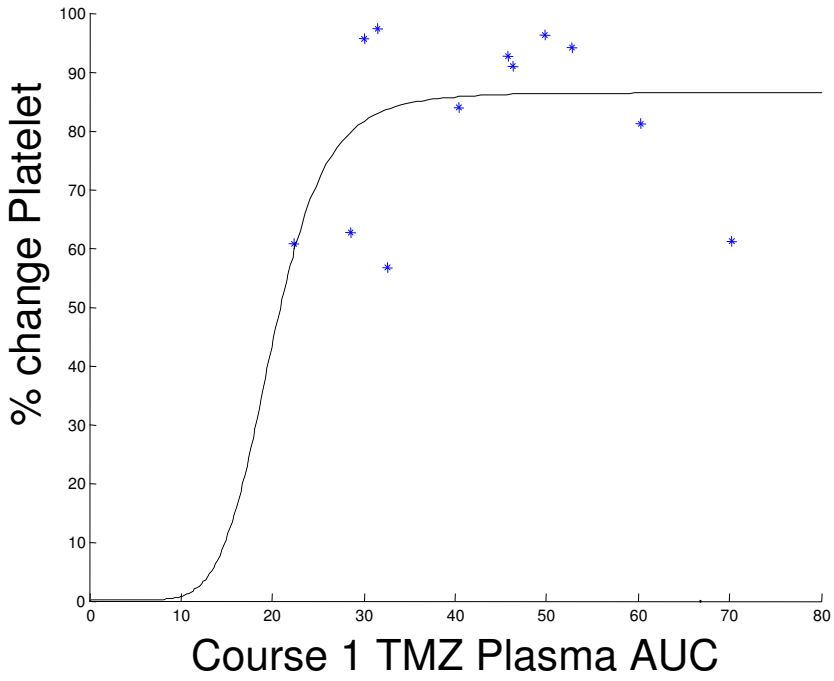
$$E_{dir} = \frac{C^{\gamma_1}}{C_{50}^{\gamma_1} + C^{\gamma_1}}$$

$$AUCE_{dir} = \int_0^{\infty} E_{dir}\, dt$$

$$E_{obs} = \frac{E_{obs,\max} \cdot AUCE_{dir}^{\gamma_2}}{AUCE_{dir,50}^{\gamma_2} + AUCE_{dir}^{\gamma_2}}$$

- AUC Model: γ_1=1 and C_{50}>>C.
- Threshold Model: γ_1=∞ and C_{50}=threshold concentration.


% change ANC
Course 1 TMZ Plasma AUC
0
10
20
30
40
50
60
70
80
90
100


% change Platelet
Course 1 TMZ Plasma AUC
0
10
20
30
40
50
60
70
80
90
100

Empirical Modeling Results

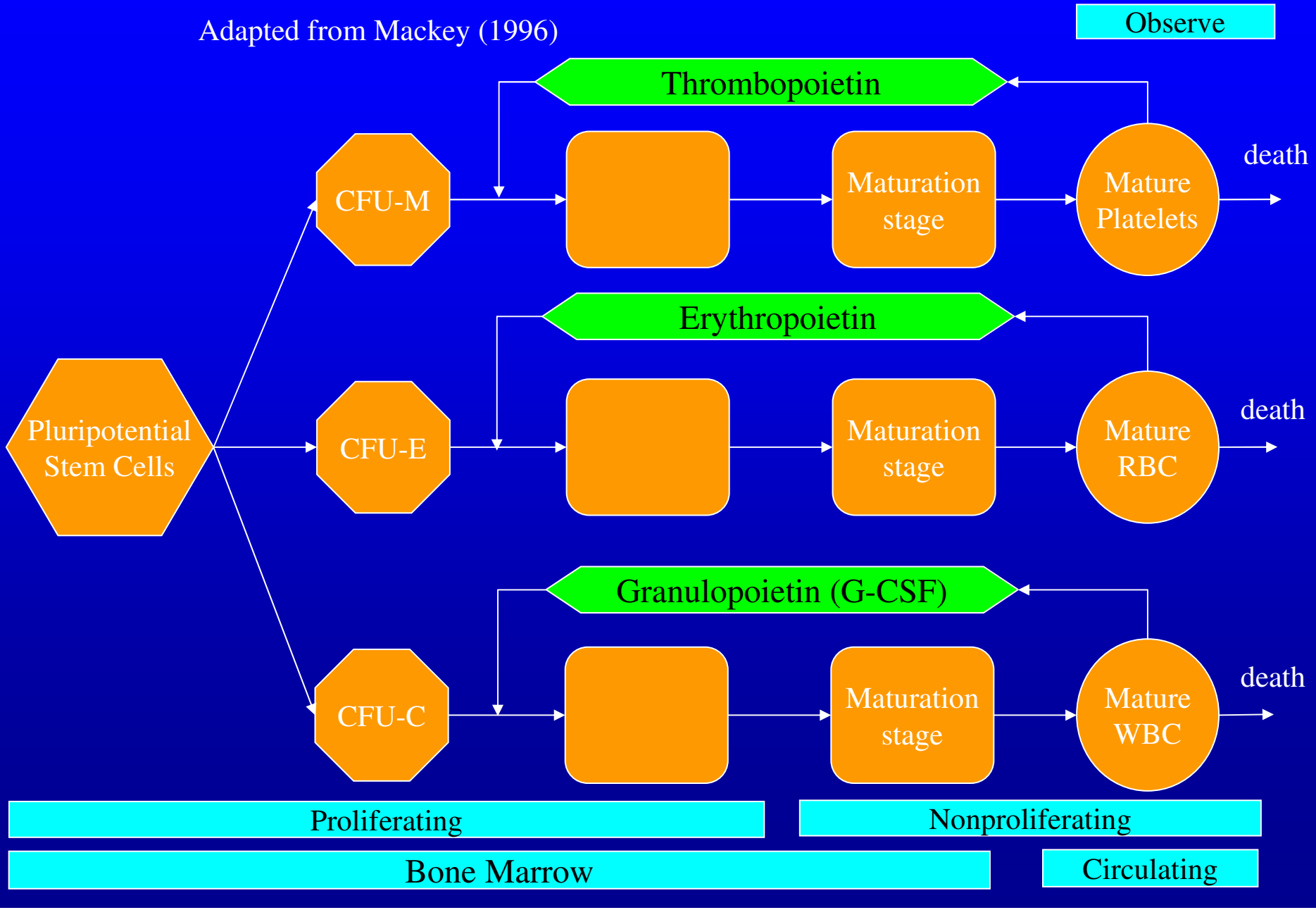
- Relationship between PK and PD effect is **not** strong.
  - This could be due to all patients received a similar fixed dose. But, TMZ AUC: ~2.5 fold
  - Even when there is a relation, the empirical model does not explain why.
- Empirical models are **not** predictive.

Mechanistic Models

- Describe the effects of chemotherapeutic drugs such as TMZ, TPT etc. on neutrophil production via a dynamical system.
- There have been a variety of mathematical models to describe hematopoiesis over the last 25 years. (S. I. Rubinow and J. L. Lebowitz; M. C. Mackey *et al.*; Shochat, Stemmer, and Segel; Panetta *et al.*; Minami *et al.*; Friberg *et al.*; Zamboni *et al.*)
- By better understanding the mechanisms of haematopoiesis we can obtain a better understanding of possible causes of myelosuppression.

Haematopoietic Regulation

Adapted from Mackey (1996)



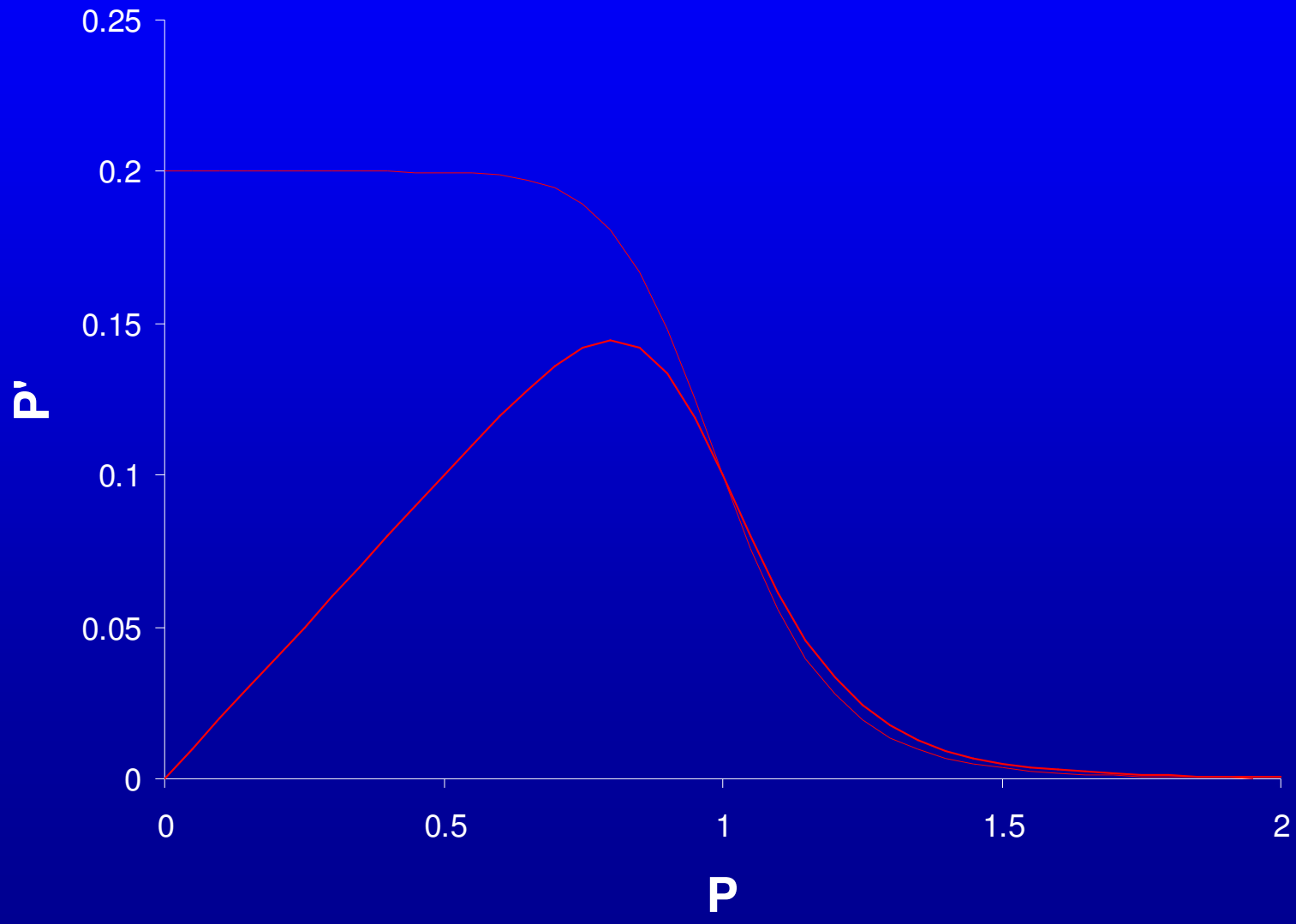
Mackey and Glass Model (Science 1977)

- Homogeneous Population of mature circulating cells of density P
- Delay $P_\tau = P(t-\tau)$ between initiation of cellular production in the bone marrow and the release of mature cells into the blood.

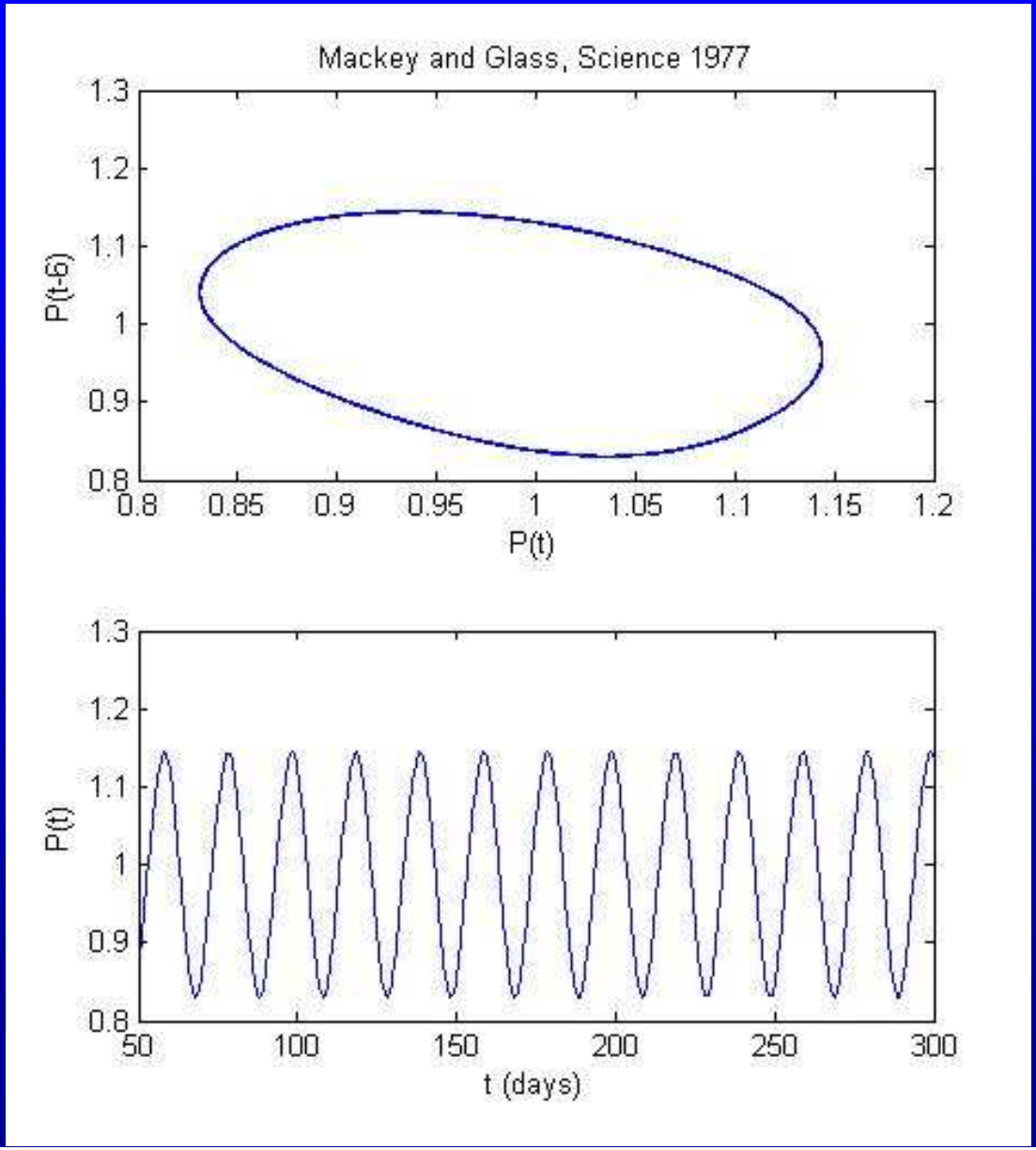
$$\frac{dP}{dt} = \frac{\beta_0 \theta^n}{\theta^n + P_\tau^n} - \gamma P$$

$$\frac{dP}{dt} = \frac{\beta_0 \theta^n P_\tau}{\theta^n + P_\tau^n} - \gamma P$$

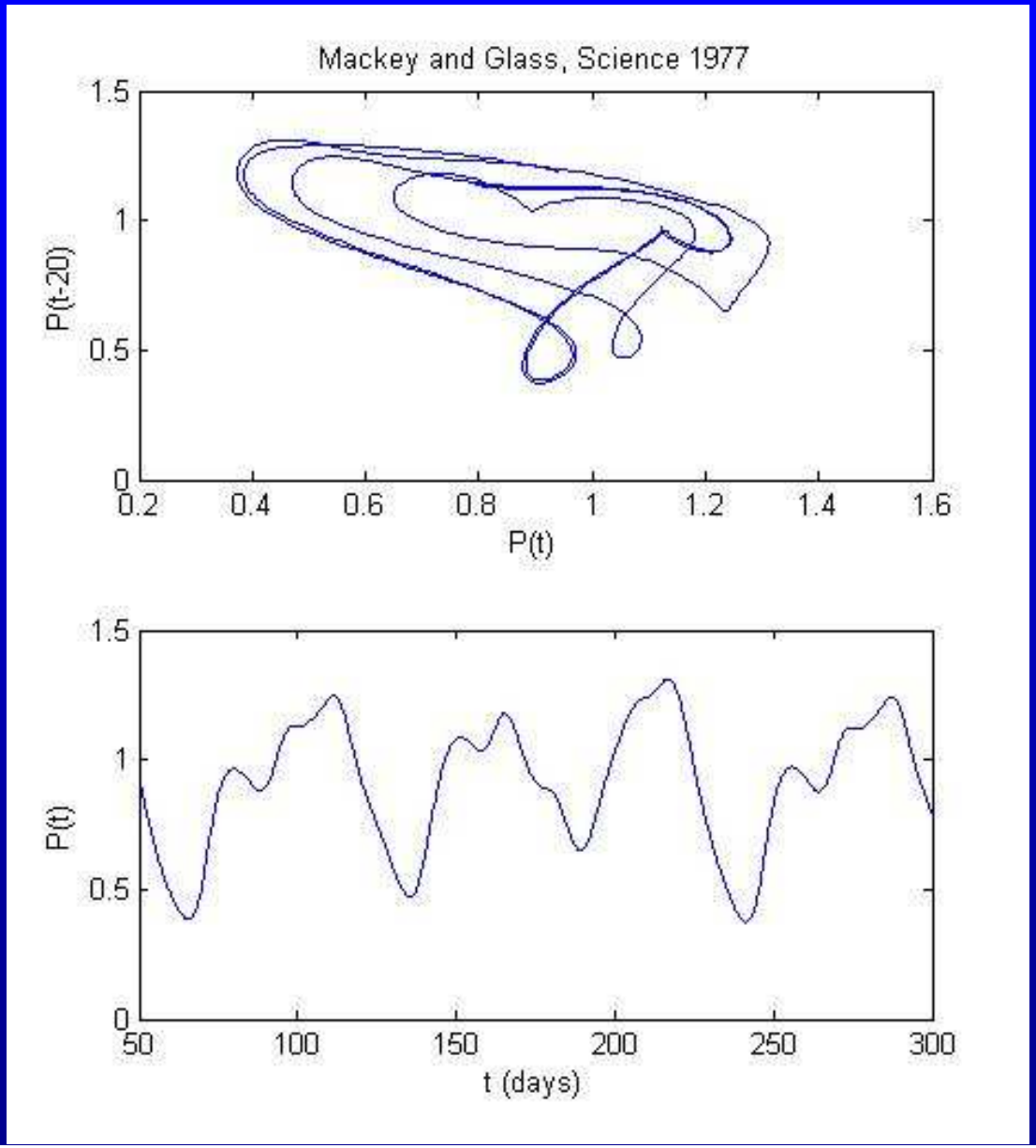
Growth Terms



Delay=6 days

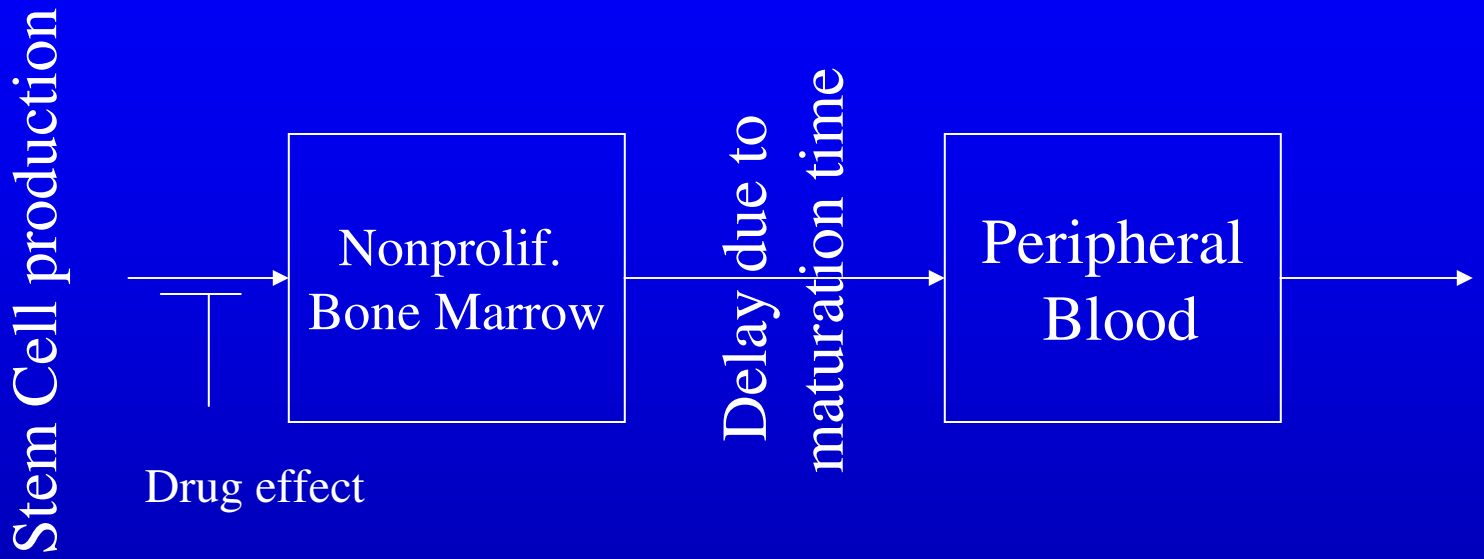

Mackey and Glass, Science 1977
P(t-6)
P(t)
1.3
1.2
1.1
1
0.9
0.8
0.8
0.85
0.9
0.95
1
1.05
1.1
1.15
1.2
P(t)
t (days)
50
100
150
200
250
300

Delay=20 days



Minami *et al.*

Clin. Pharmacol. Ther. (64) 1998



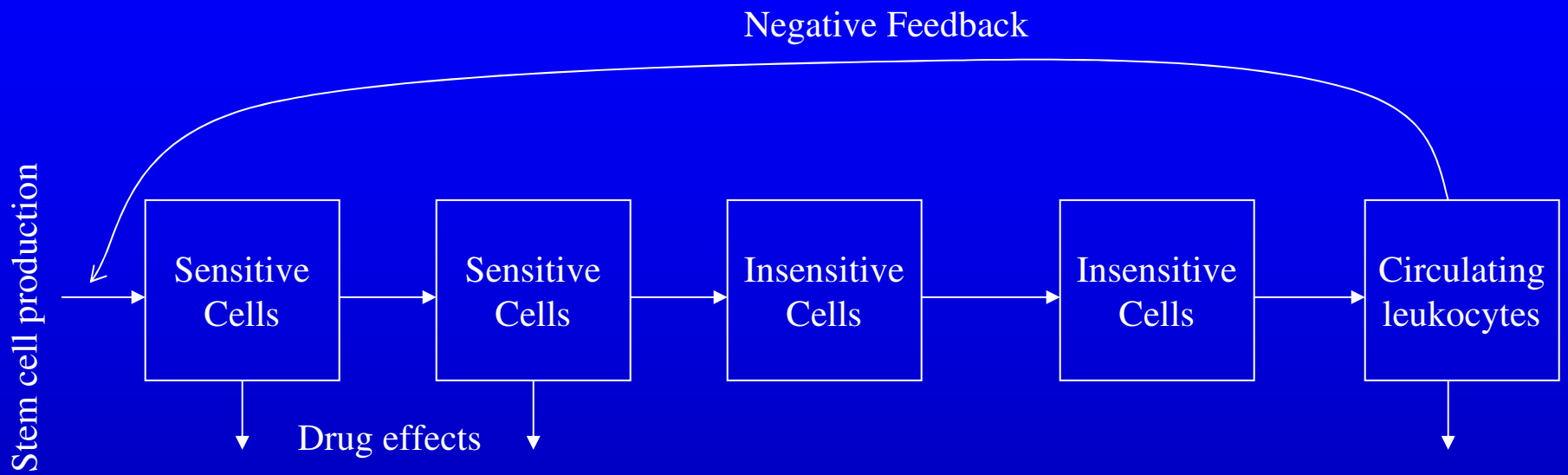
- Used to describe leukopenia due to Paclitaxel and etoposide
- Drug effect **blocks** stem cell production
- Stem cell pool unaffected by drug
- No feedback term included

Negative Feedback

- An inverse relation has been observed between circulating neutrophil density and serum levels of granulocyte colony stimulating factor (G-CSF). (Kearns *et al.* J. Pediatr. 123)
- Administration of exogenous G-CSF leads to:
  - increased peripheral neutrophil counts
  - increased amplitude of oscillations
  - decreased period of oscillations
  - decreased average maturation time
- Can lead to oscillations in the ANC.
  - See multiple references by Mackey *et al.*

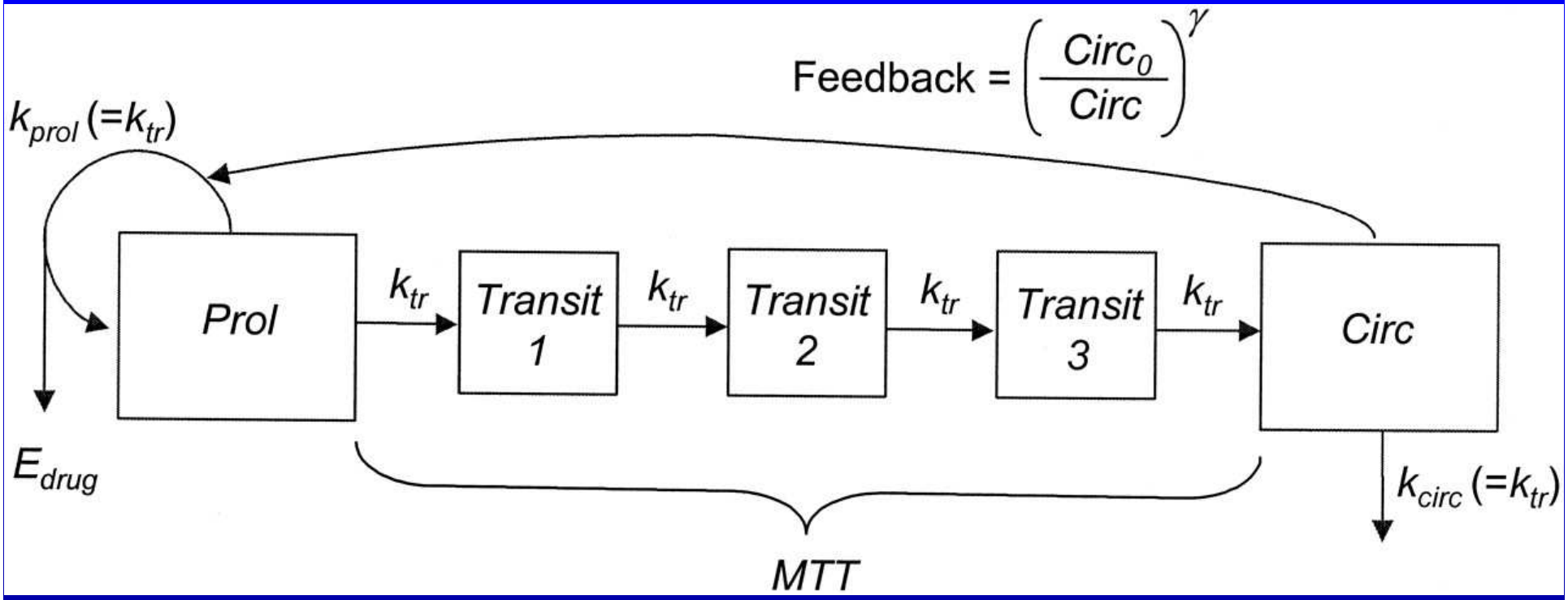
Friberg *et al.*

J. of Pharmacol. Exp. Ther. (295) 2000



- Used to describe the toxic effects of 5-FU in mice
- Negative feedback from circulating leukocytes affects stem cell production
- Drug effect **kills** sensitive cells (i.e. cells that are proliferating) in the B.M.
- Drug effect does **not** block stem cell production
- Stem cell pool unaffected by drug

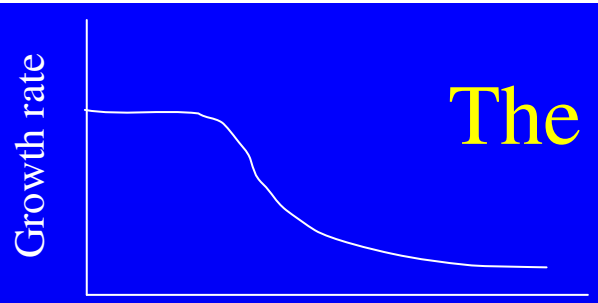
Friberg, L. E. et al. J Clin Oncol; 20:4713-4721 2002



Used to model myelosuppression patterns due to the following drugs:

- Docetaxel
- Paclitaxel
- Etoposide
- 2'-deoxy-2'-methylidenecytidine (DMDC)
- irinotecan (CPT-11)
- vinflunine

The Mechanistic Model For TMZ



Kirstein *et al.* Proc Amer Soc Clin Oncol, 20, 2001

Panetta *et al.* Math. Bio. 186(1): 29-41, 2003

Growth rate

Proliferating Bone Marrow

k_1

Non-proliferating Bone Marrow Compartment 1

k_2

Non-proliferating Bone Marrow Compartment 2

k_3

Drug Effect

k_4

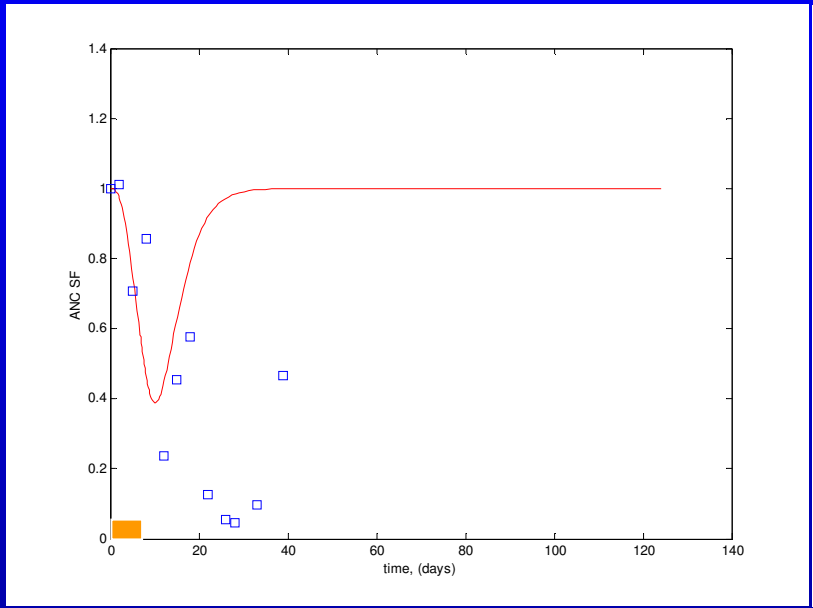
Peripheral Neutrophils

G-CSF signal

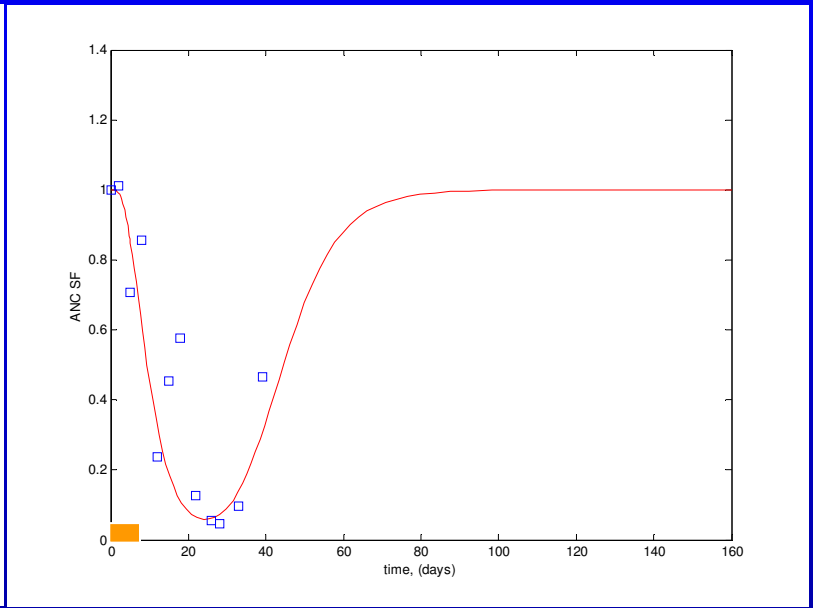
- Drug effects are cytotoxic to stem cells
- Negative feedback from circulating leukocytes affects stem cell production

Drug Effects

TMZ blocks stem cells



TMZ cytotoxic to stem cells



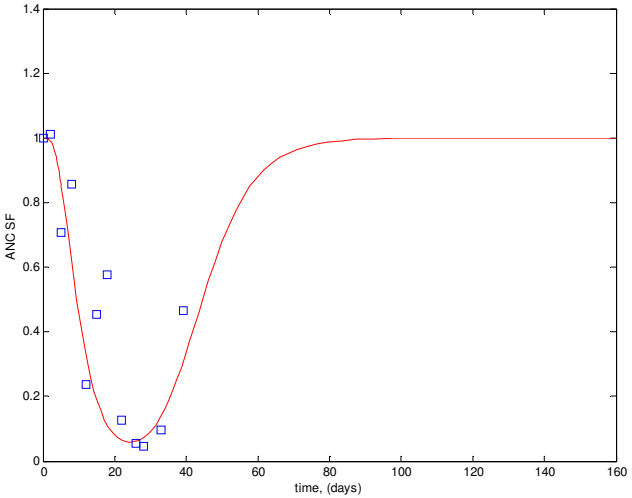
Note: To obtain a better description of the data when TMZ only blocks stem cells, the drug would have to be active ~6× longer than is realistic

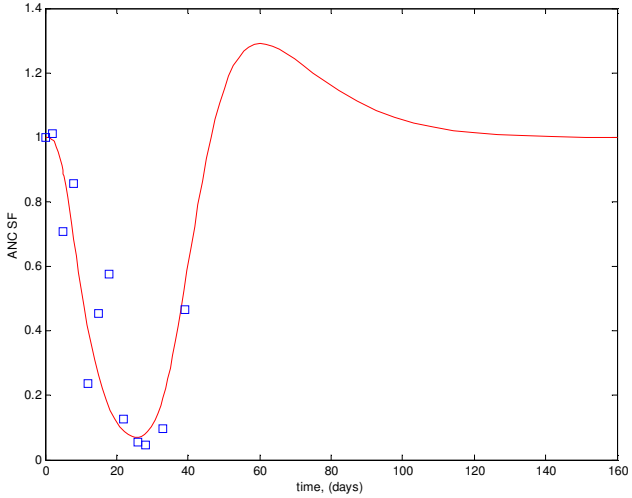
Qualitative effects of G-CSF feedback

No Feedback

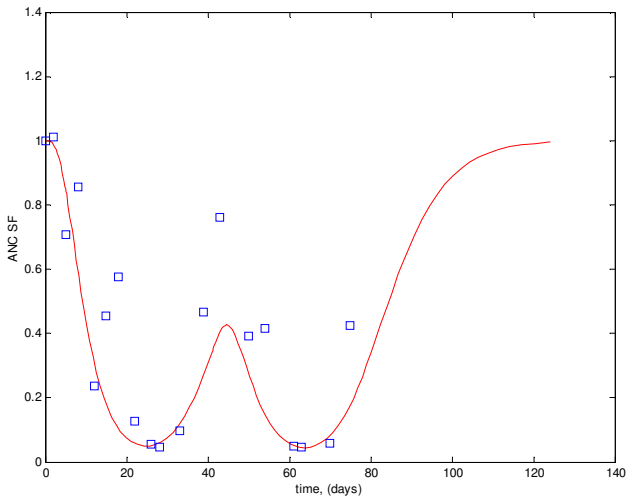
Feedback

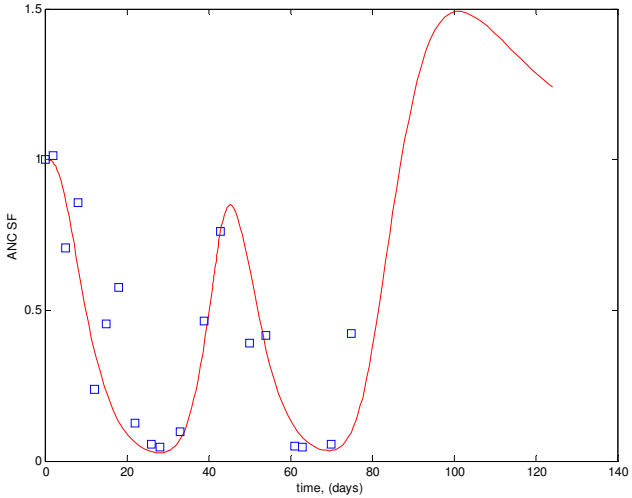
Single Dose



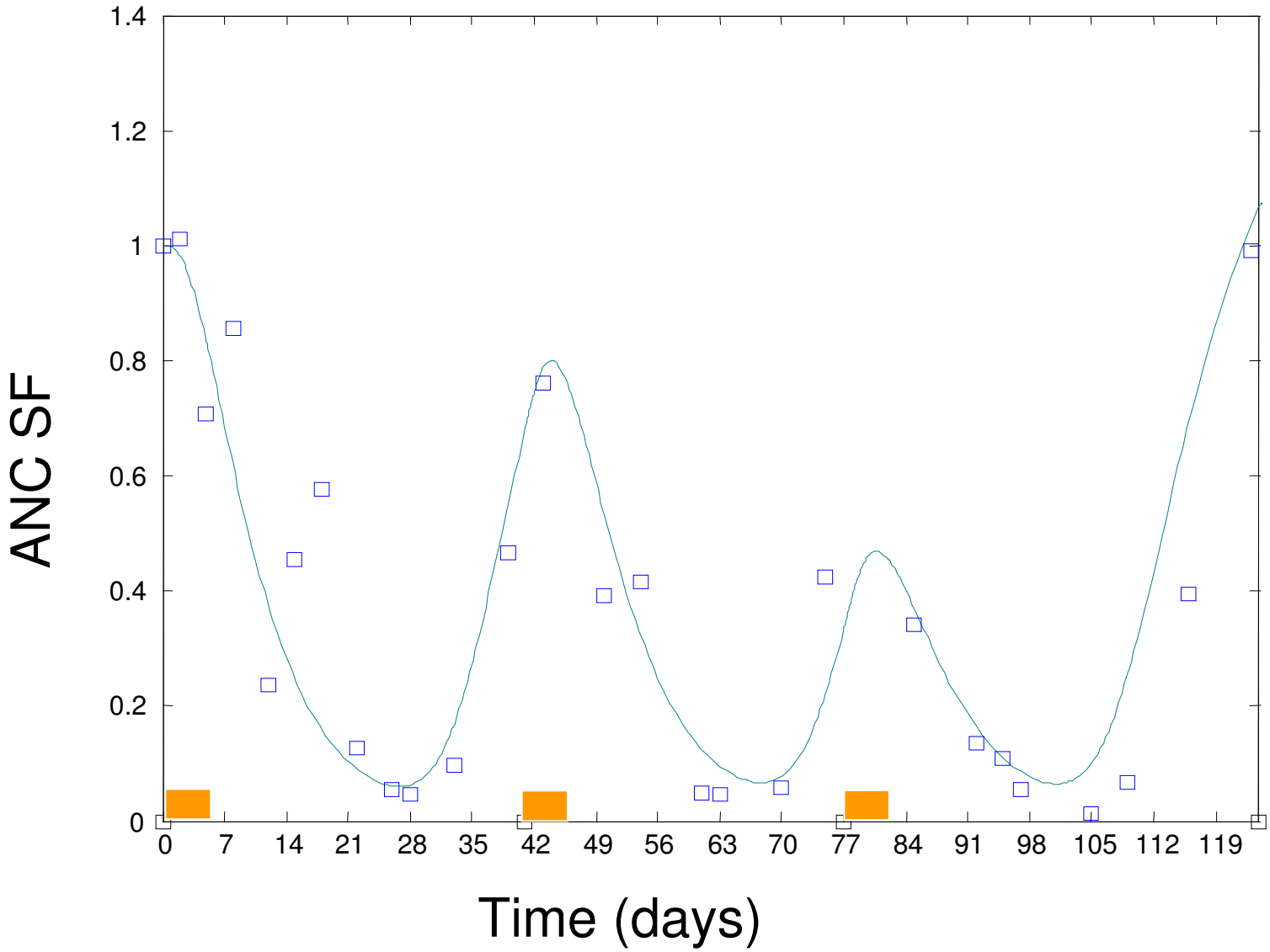


Two Doses

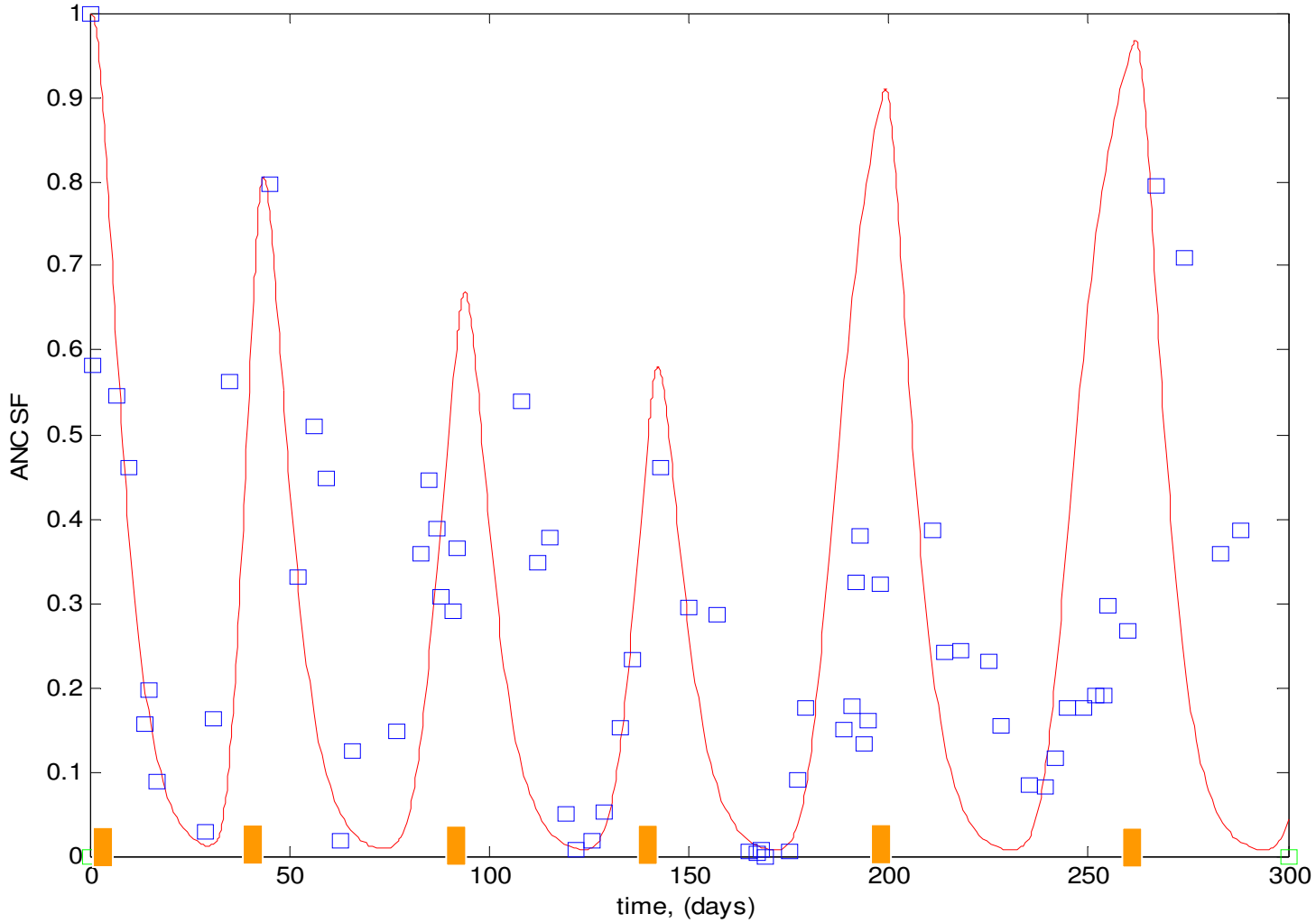




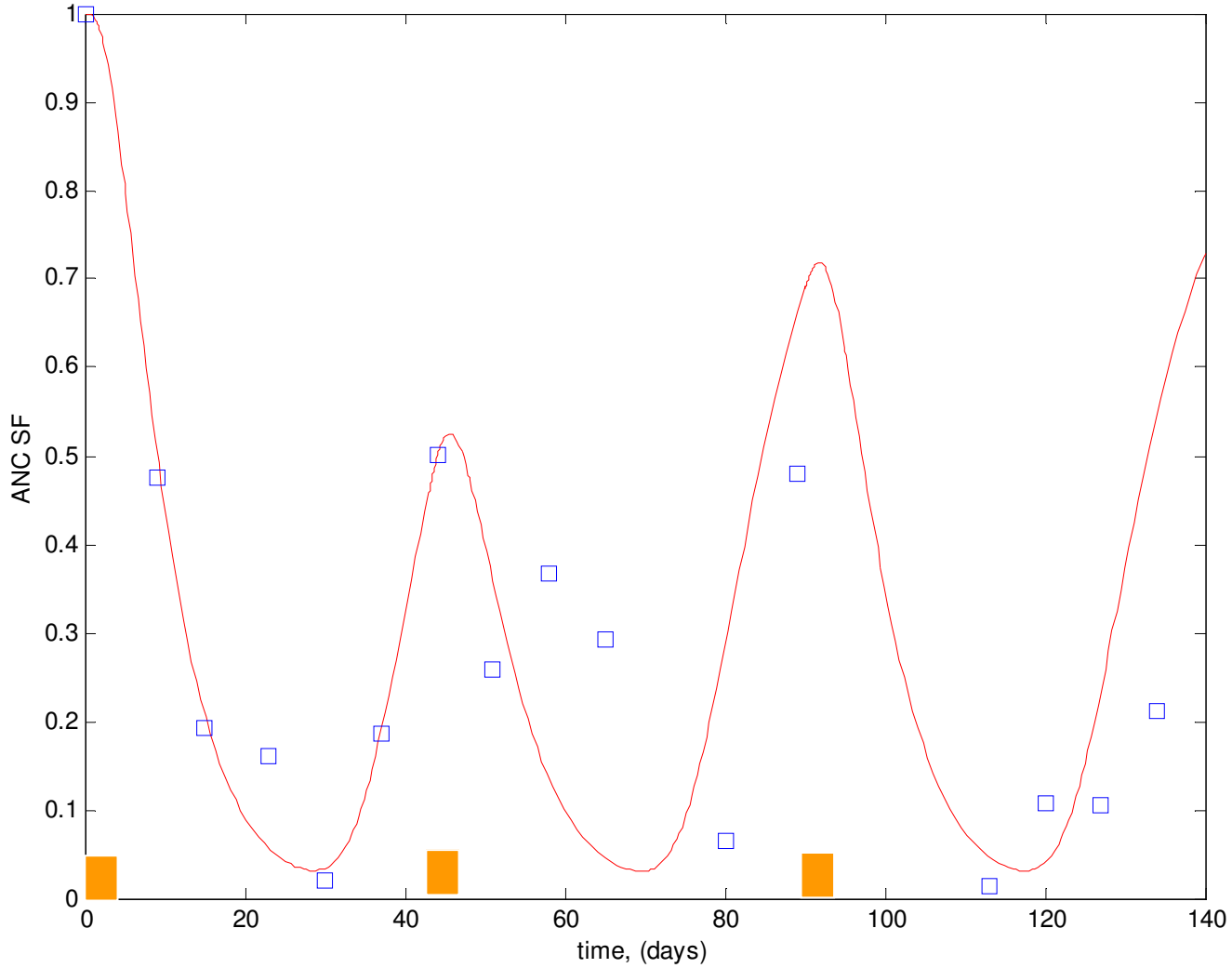
- Predict Courses 2 and 3 from Course 1



- Predict Course 2 from Course 1
- Predict Course 3-6 from Courses 1 and 2

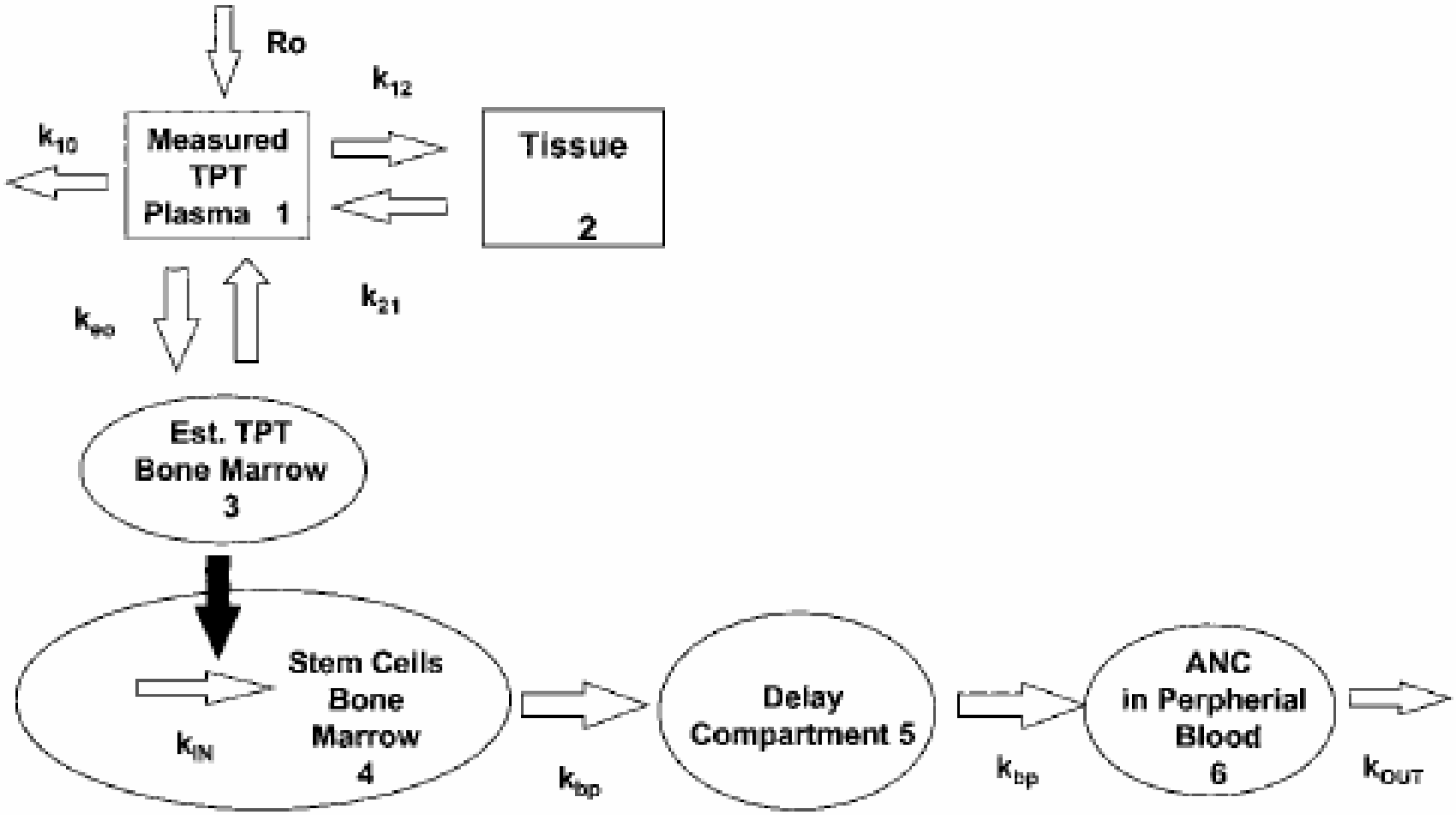


Predict course 2 and 3 from course 1

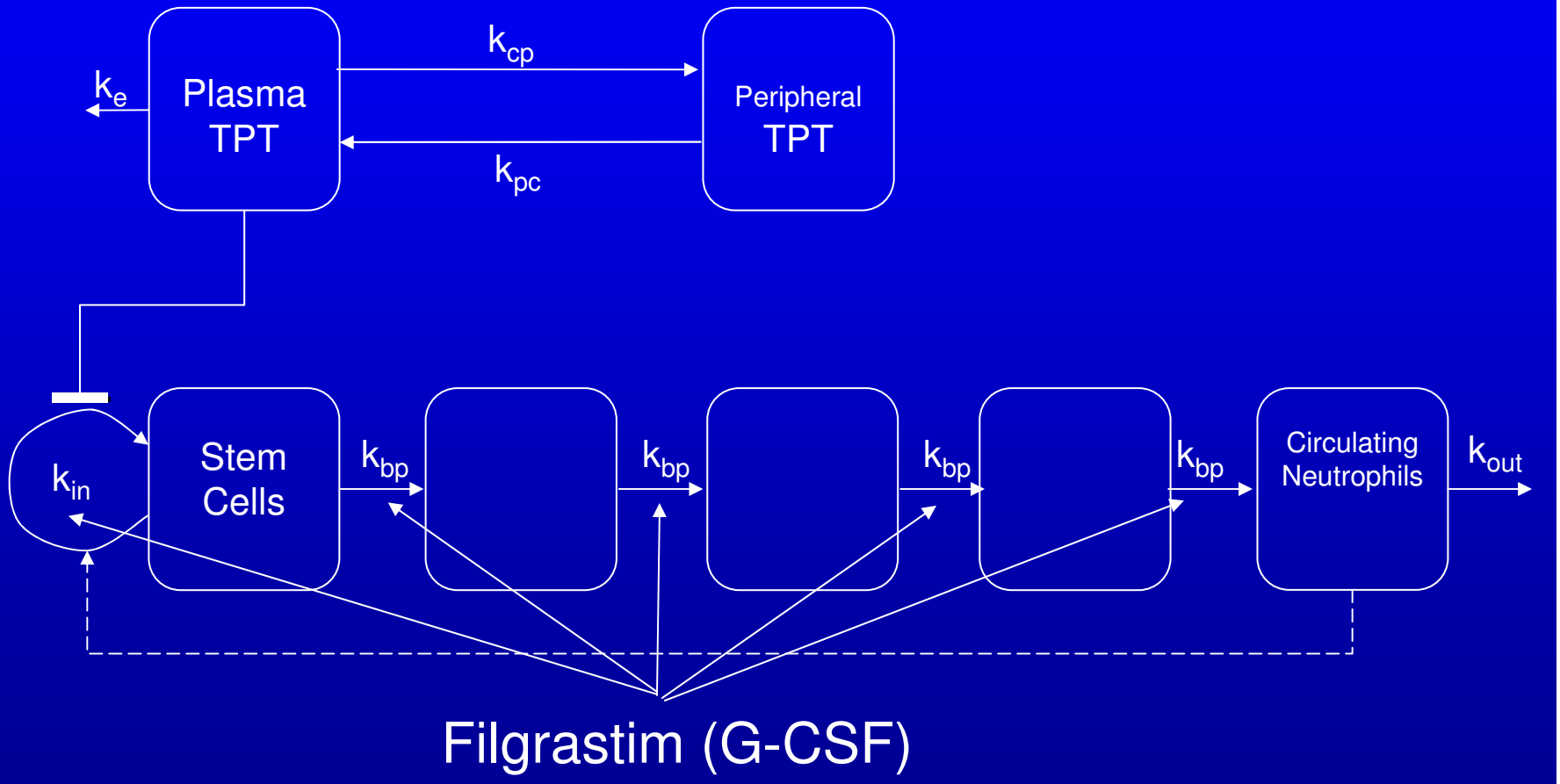


Model for TPT with constant rate k_{in}

(Zamboni *et al., CCR 2001*)



Modified TPT Model with 1st order k_{in}



The Equations

$$\frac{dX_c}{dt} = -\left(k_e + k_{cp}\right) X_c + k_{pc} X_p$$

$$\frac{dX_p}{dt} = k_{cp} X_c - k_{pc} X_p$$

Pharmacokinetics

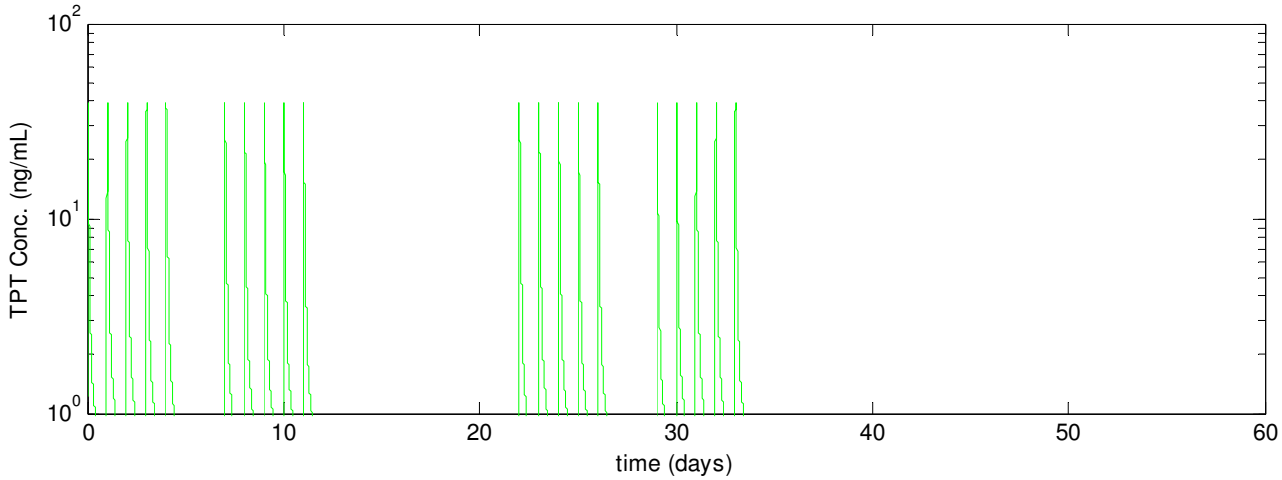
$$\frac{dN_p}{dt} = \left(k_{in} \left(N_{circ} \right) \left[\frac{IC_{50}}{IC_{50} + X_c / V} \right] - k_{bp} \right) N_p$$

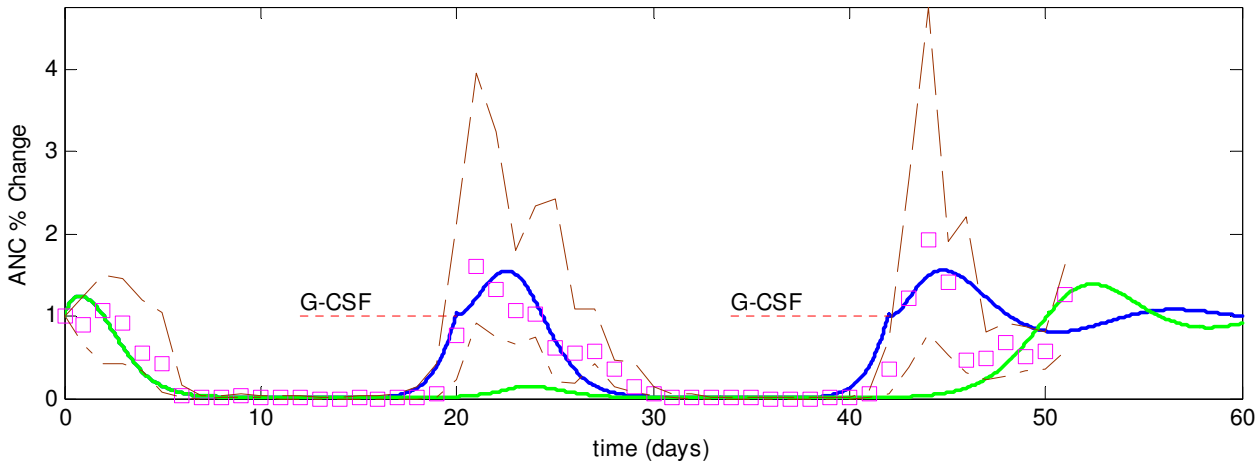
$$\frac{dN_{d1}}{dt} = k_{bp} \left(N_p - N_{d1} \right), \quad \frac{dN_{d2}}{dt} = k_{bp} \left(N_{d1} - N_{d2} \right), \quad \frac{dN_{d3}}{dt} = k_{bp} \left(N_{d2} - N_{d3} \right)$$

$$\frac{dN_{circ}}{dt} = k_{bp} N_{d3} - k_{out} N_{circ}$$

Pharmacodynamics

Median Parameters:
based on fits to 27 patients





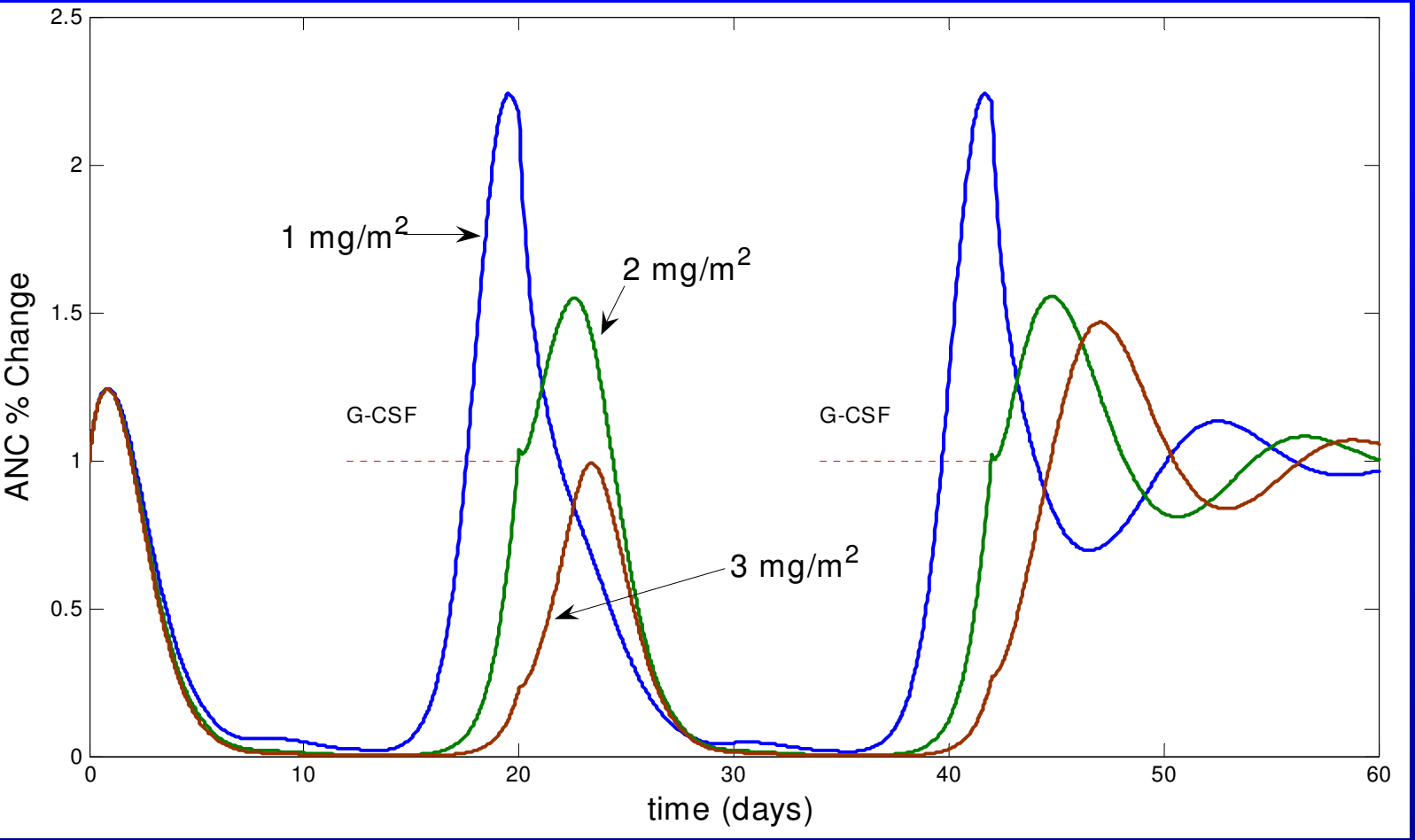
Parameters are more physiological in 1st order version.

- **IC_{50} (concentration with 50% effect)**
  - 1.2 ng/ml in human CFU-GM cells (Parchment, 1997)
  - Constant k_{in} model median (range): 3.9×10^{-3} (1.0×10^{-5}, 5.2×10^{-3}) ng/ml
  - First-order k_{in} model median (range): 0.54 (0.001, 2.4) ng/ml

Additional model results

- **Transient time (defined by $4/k_{bp}$)**
  - Normal bone marrow ~5 to 6 days
  - median (range): 2.5 (1.4, 5.4) days
- G-CSF effects
  - Decreased recovery time to baseline by ~1 week
  - Increased k_{in} by a median of 58%
  - Increased k_{bp} by a median of 46%

Predictions:
Changes in TPT dose (daily x10)

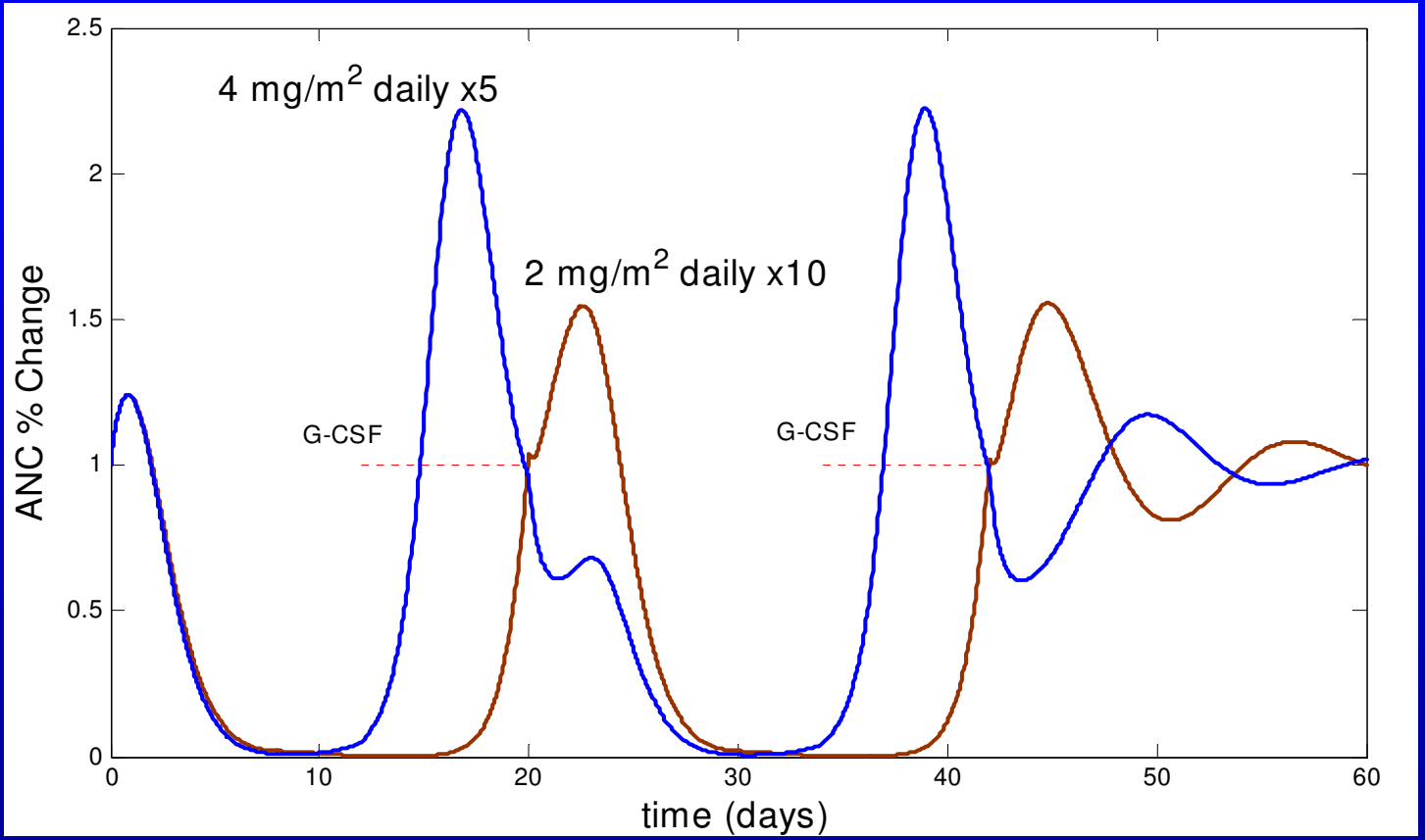


Each incremental increase in dose delays recovery of ANC by ~3 days

Predictions:

Changes in TPT Schedule (5 vs 10 days)

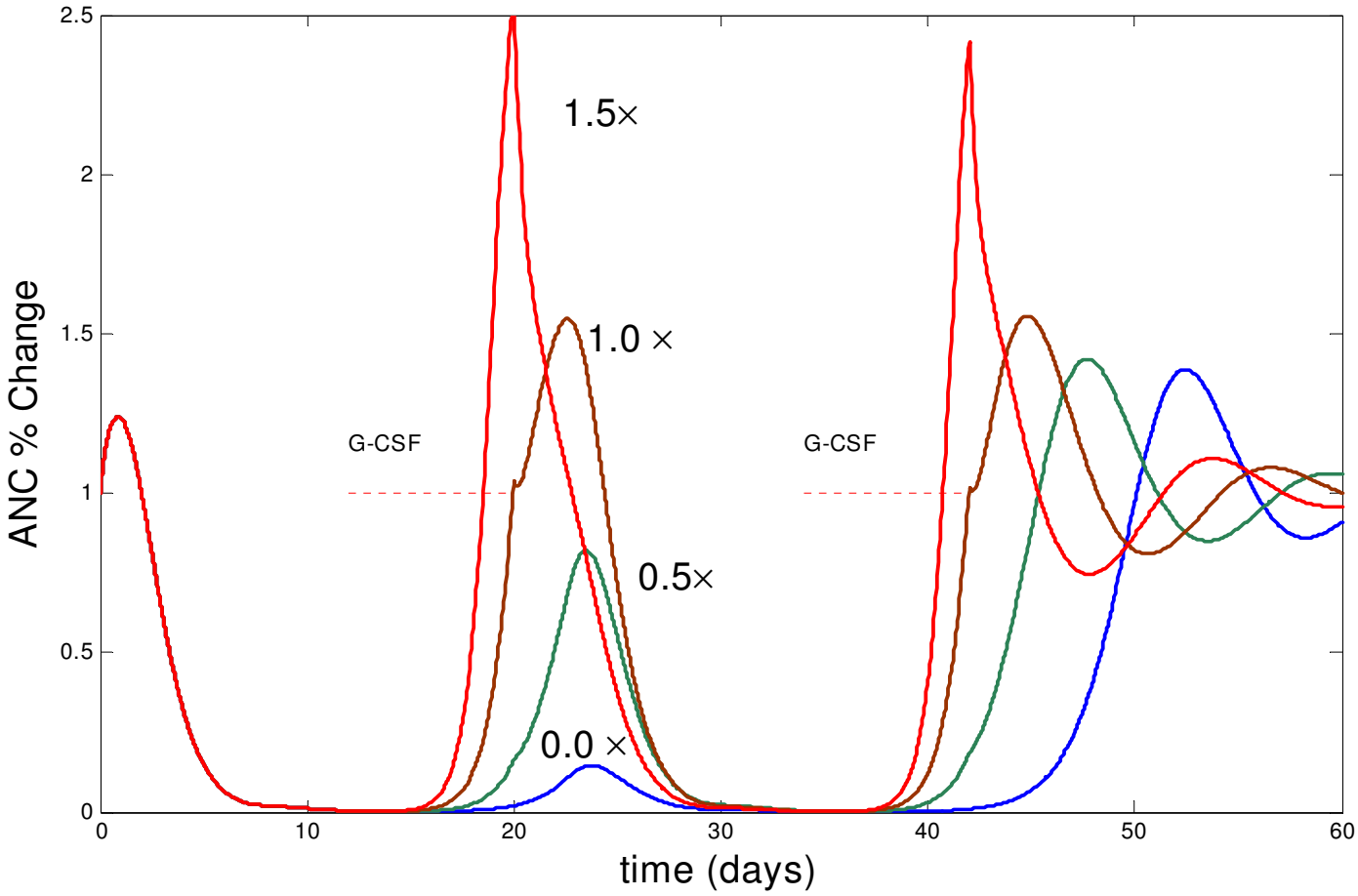
Same total dose of 20 mg/m^2 per course



Difference in ANC recovery time ~5 days

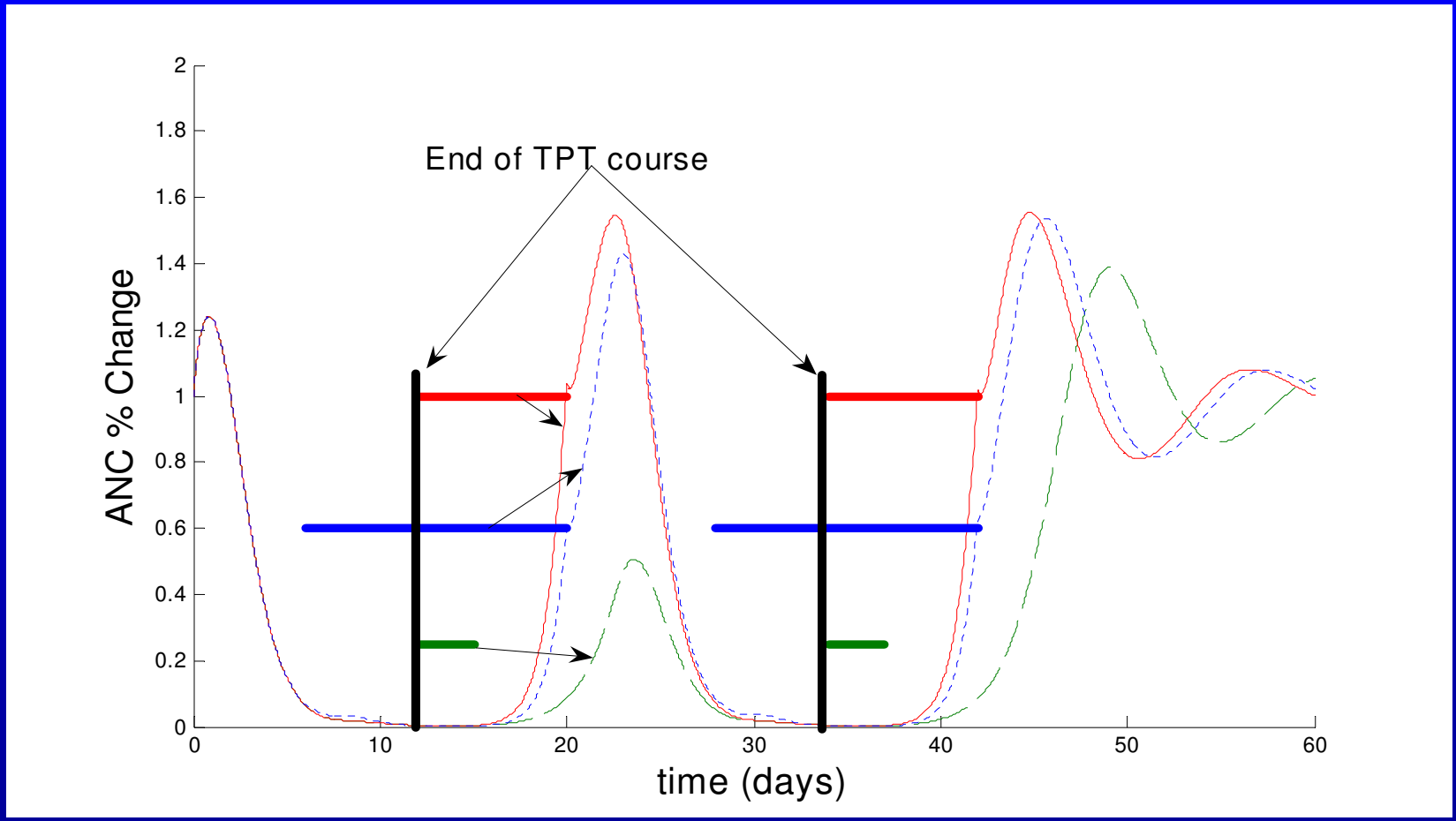
Predictions:

Changes in an exogenous G-CSF dose of 5 μg/kg/day



- Decreased duration by ~7days (1x to 0x)
- Decreased duration by ~3days (1x to 0.5x)
- Increased duration by ~1 day (1.5x to 1x)

Predictions:
Changes in exogenous G-CSF duration



Starting G-CSF treatment earlier did not significantly alter recovery

Conclusions

- Mechanistic models can explain the data more appropriately relative to empirical models
- 1st order stem cell production is physiologically more reasonable in the drugs we have considered
- Endogenous G-CSF effects are necessary.
- The models have shown predictive abilities which can be helpful in designing treatment regimens.