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# Optimizing Topotecan Therapy in Pediatric Neuroblastoma


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# Clinical Activity of TPT
# Neuroblastoma

- 60% response rate (CR+PR) with a median (range) tumor reduction of 58% (5%, 95%). (Santana *et al.* JCO 2005)
  - Dosed daily for 10 days
  - *Individualized dose*: target TPT plasma AUC of 80 to 120 ng/ml·hr. Median dose of 2.7 mg/m$^2$
- 39% response rate (POG, Kretschmar *et al.* JCO 2004)
  - Dosed daily for 5 days
  - *Traditional dose* of 2 mg/m$^2$

# Dose Individualization

- Large inter-individual variability (12 fold range in systemic clearance) in TPT Clearance in children with cancer.
- It has been shown in xenograft mice that the minimum TPT systemic exposure to achieve a CR in 4 of 6 NB models was an AUC of 88 ng/ml·hr

Zamboni *et al.* JNCI 1998

# Clinical Activity of TPT
# Refractory Acute Leukemia

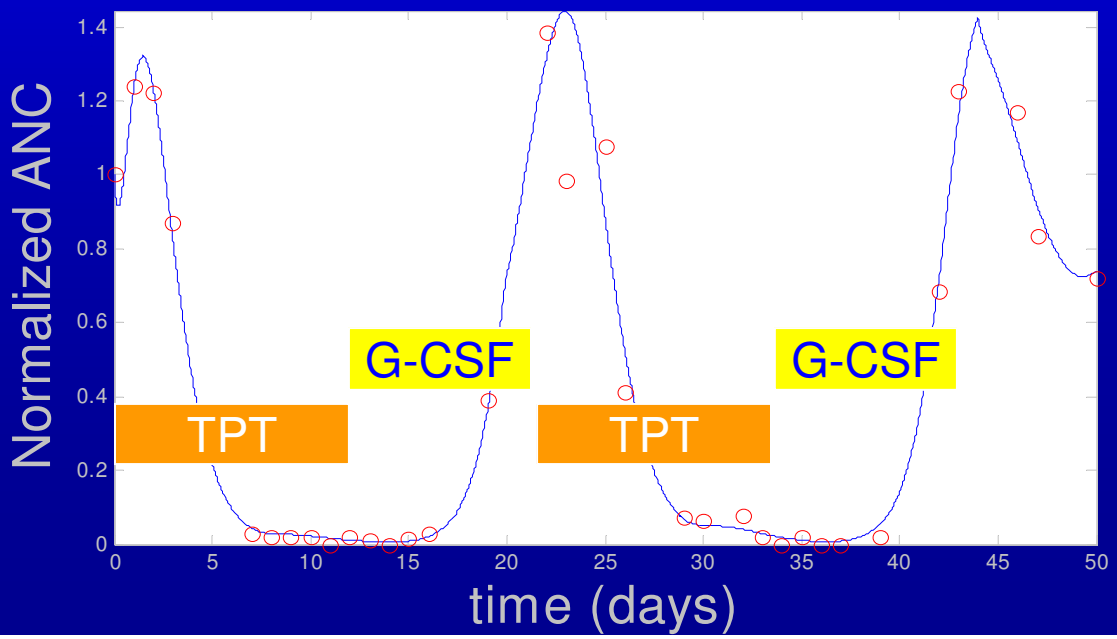
- 6 of 18 (CR+PR) in patients dosed with 1.4-2.4 mg/m$^2$ over 12 days.
- 2 of 31 (CR+PR) in patients dosed with 2-5.2 mg/m$^2$ over 5 to 9 days.
  - The two positive responses were dosed over 5 and 9 days.

Furman *et al.* JCO 2002

# TPT Toxicities

## Neuroblastoma (Santana *et al.* JCO 2005)

- **Grade 4 neutropenia**: occurred in all patients;
  median length (range) 15 days (8-22).
- **Grade 4 thrombocytopenia**: occurred in all but 1 patient
- **Grade 4 diarrhea**: 6 episodes of 56 TPT cycles



# Dosage and Schedule are Clinically Relevant Factors

- TPT is a topoisomerase I inhibitor (cell-cycle specific)
- Mathematical models of cell-cycle specific drugs suggest longer schedules to be more efficacious but also more myelosuppressive

  - Panetta and Adam MCM 1995
  - Panetta MB 1997

Optimal Dosage and Schedule?

# Main Modeling Aim

- Develop an optimal treatment in terms of TPT and/or G-CSF dose/schedule that:
  - **Maximizes efficacy**. Defined by a reduction in tumor volume over a predefined interval
  - **Effectively manages toxicities**. Defined by a
    - minimum acceptable ANC level
    - maximum length of ANC depletion
    - and/or maximum TPT exposure.

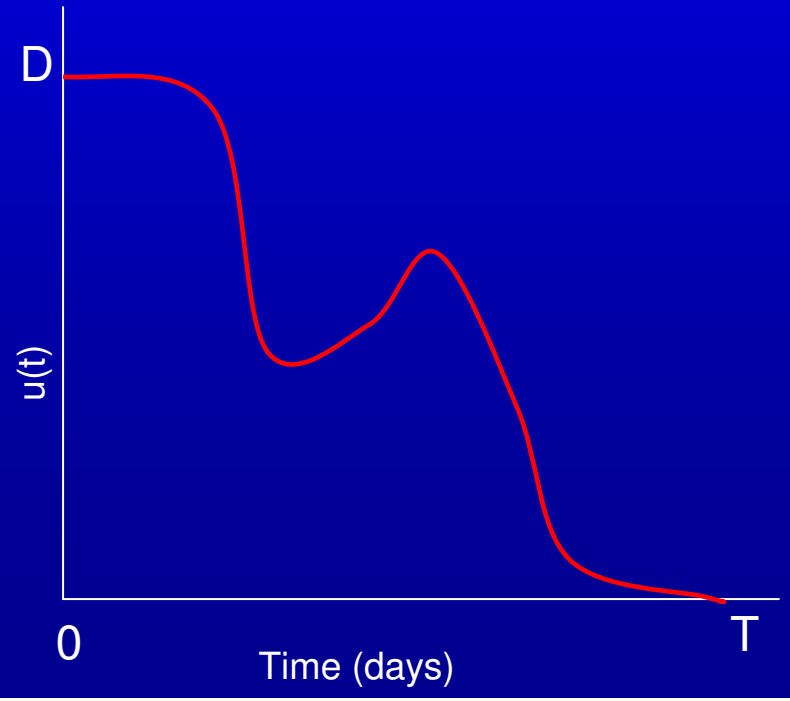
# Examples of treatment functions:

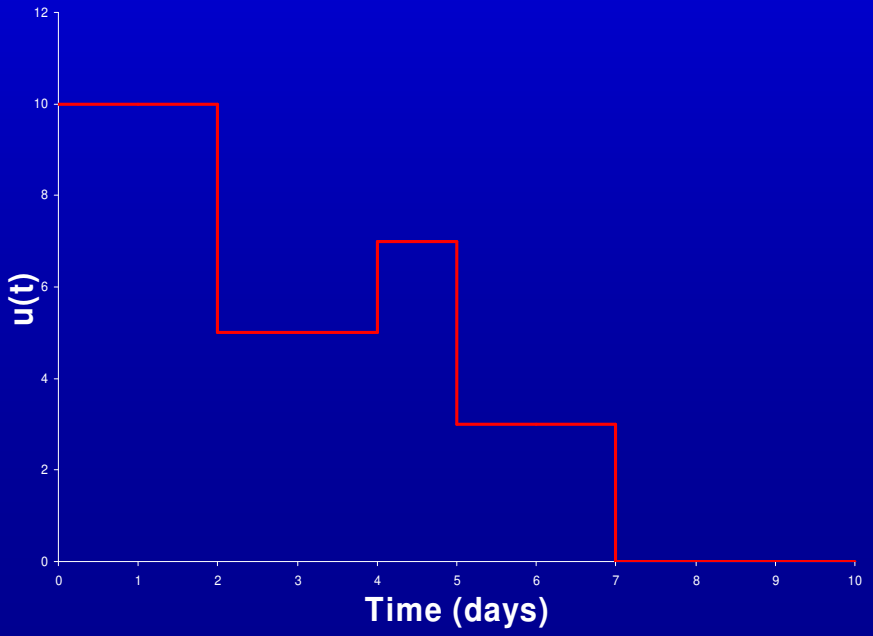
General form:

$$\{u(t) \text{ measurable} \mid 0 \le u(t) \le D,\ t \in [0,T]\}$$

Piecewise constant form:

$$u(t) = \begin{cases} D_i / t_i & \text{for } 0 \le t < t_i \\ D_i / (t_i - t_{i-1}) & \text{for } t_{i-1} \le t < t_i \end{cases}$$



# Examples of Objective Functions

Traditional optimal control forms: (Fister and Panetta SIAM J Applied Math. 2000 and 2003)

$$\min_{u(t)} J(u) = \int_0^T \left[ a\left(N - N_d\right)^2 + bu^2 \right] dt \quad or$$

$$\min_{u(t)} J(u) = aN(T) + b\int_0^T u(t)\, dt$$

Constrained optimization forms: (Iliadis and Barbolosi CBR 2000, Barbolosi and Iliadis CBM 2001)

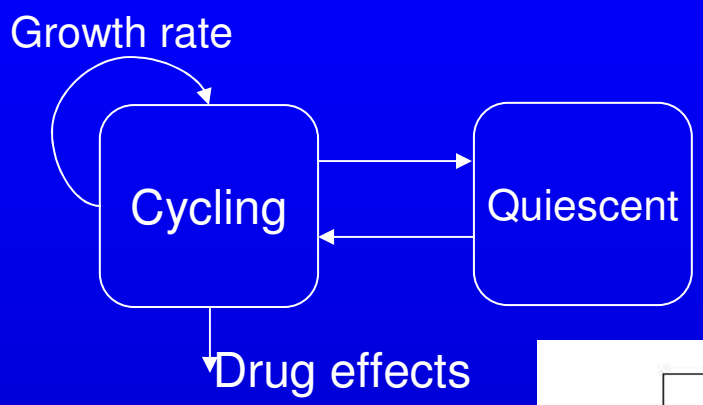
$$\min_D [N(T)] \quad or$$

$$\min_D \left[ N\left(t^*\right) \right] \quad with \quad N\left(t^*\right) = \min_{t\in[0,T]} \left[ N(t) \right]$$

Contraints

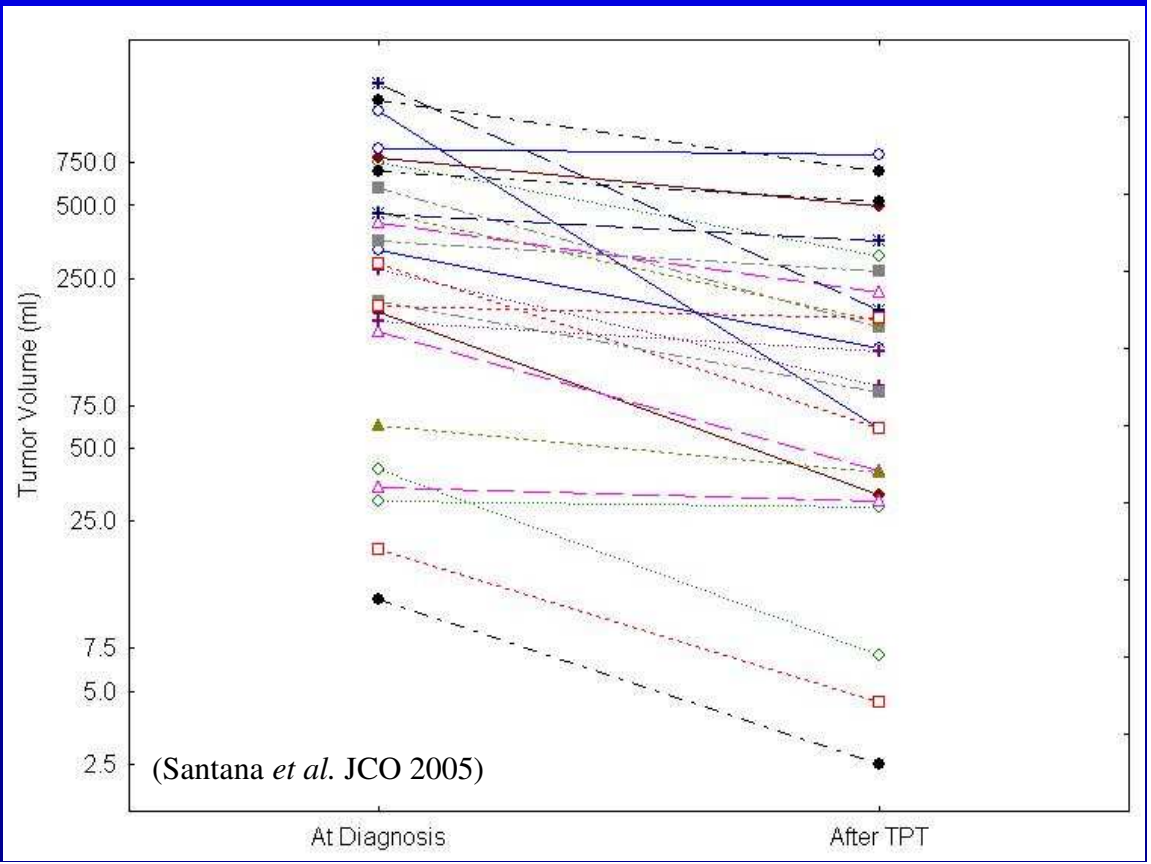
- Cons ≤ Max Conc
- AUC ≤ Max AUC
- ANC ≥ Min ANC
- Length(ANC) ≤ Max Length(ANC)

# Tumor Efficacy Model

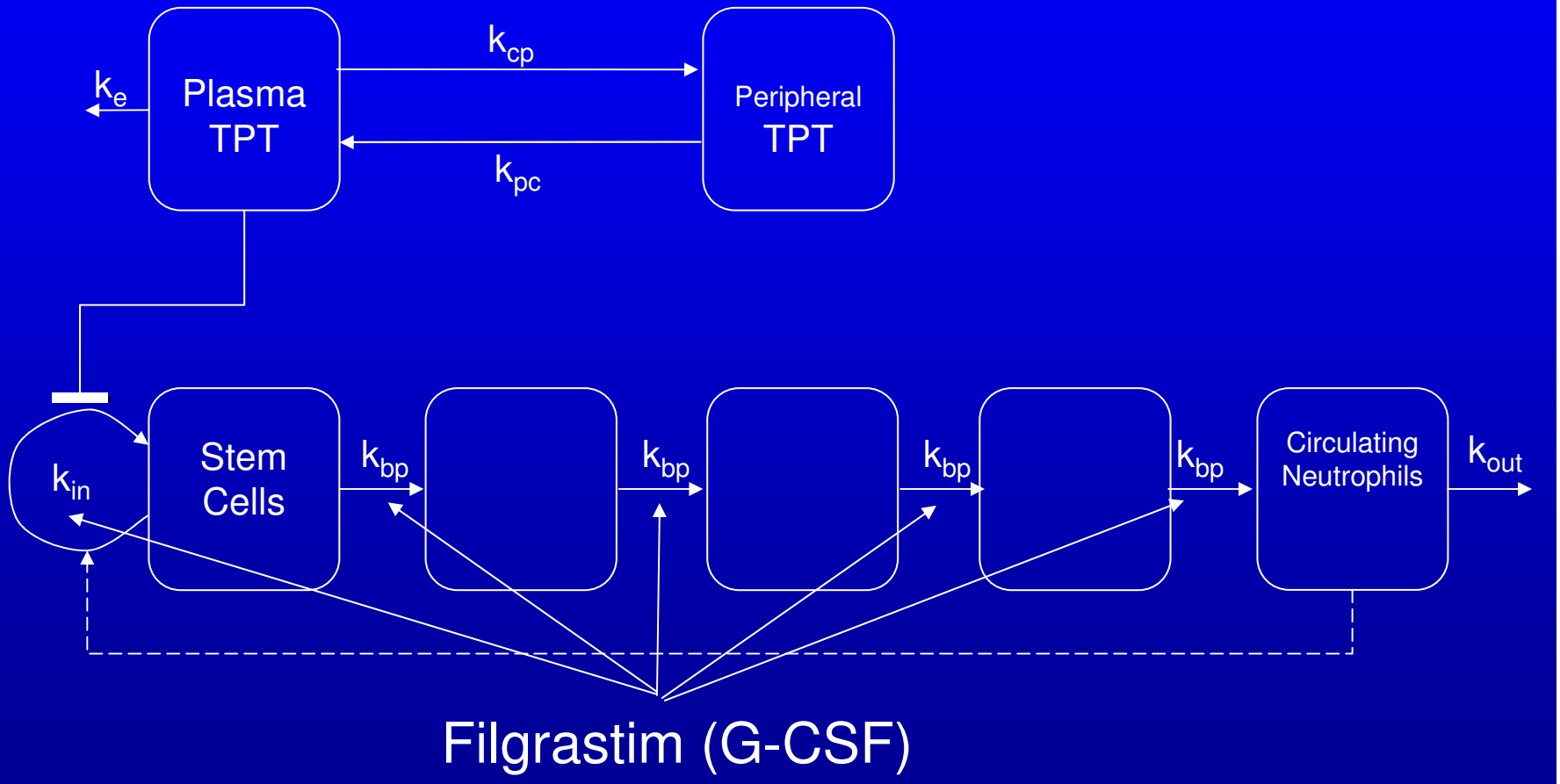



- Panetta and Adam MCM 1995
- Panetta MB 1997

Human Neuroblastoma
doubling times in Xenografts
4.7 to 18 days
Zamboni *et al.* JNCI 1998

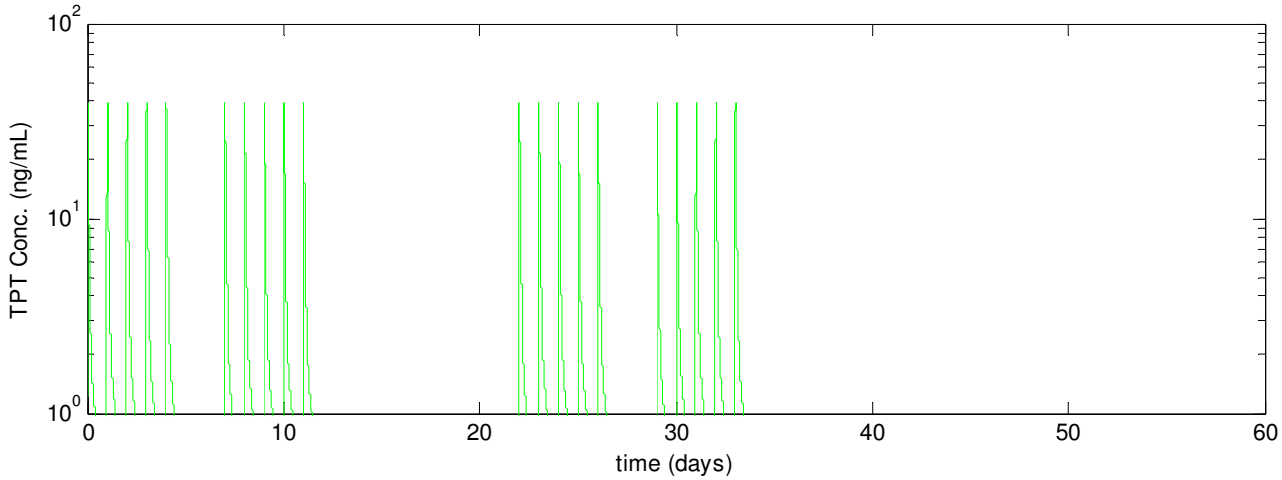


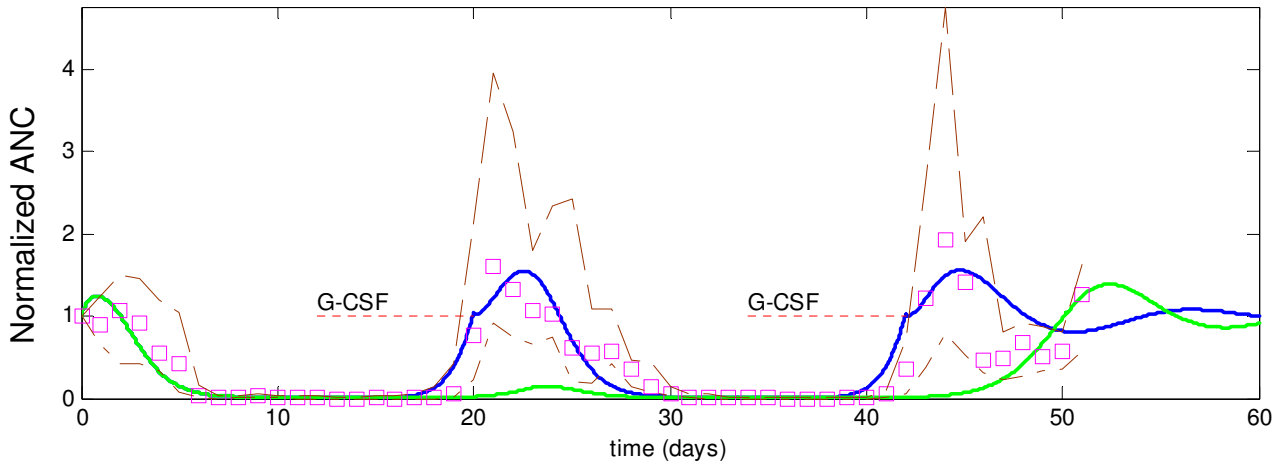
# TPT Myelosuppression Model



# Serial ANC data with model fit

## based on 27 pediatric NB patients



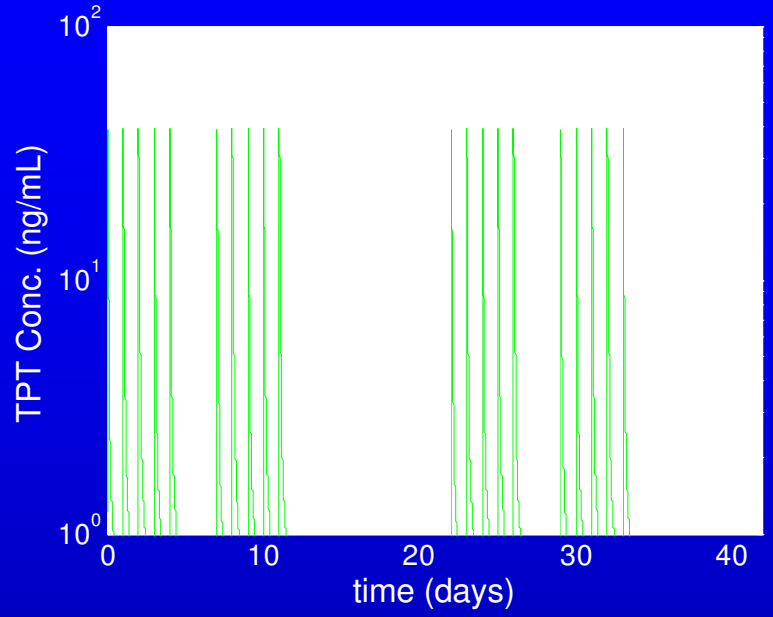
# Proposed Optimal Control Problem

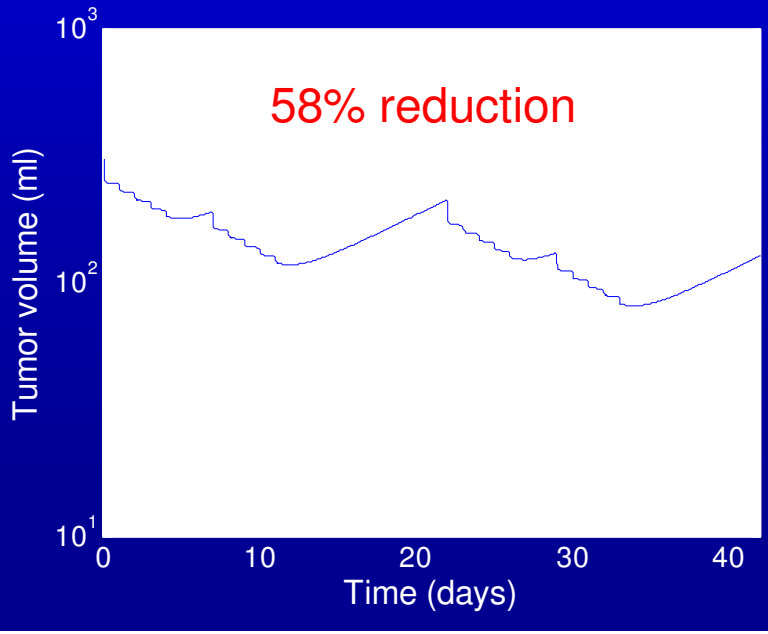
- **Minimize** tumor volume with respect to TPT and G-CSF dose/schedule
  - At the end of the second cycle (or, on the interval [0, T])
  - piecewise constant dosing
  - Note: end of second cycle: median T=58 days, (range 44 to 73 days)
- **Constraints** related to toxicities
  - Length of ANC<500 ($1/mm^3$) < $ANC_t$ } Specific constraint
  - TPT Dose < $TPT_{max}$
  - G-CSF Dose < $G\text{-}CSF_{max}$

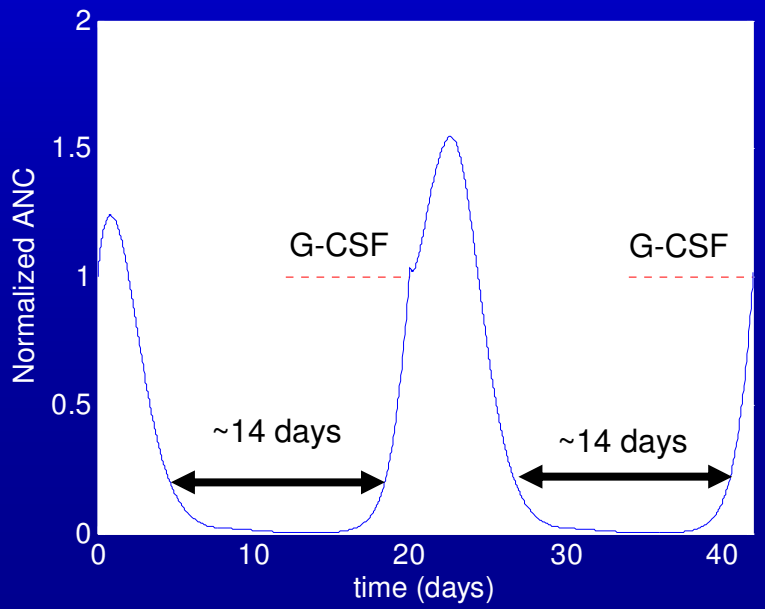
  } Generalized constraints

# Results

- Current dosing schedule:
  - TPT 2 mg/m$^2$/day daily×5×2
  - G-CSF 5 mg/kg/day daily from day 12 to 20
  - Estimated cell kill based on median data in: (Santana *et al.* JCO 2005)

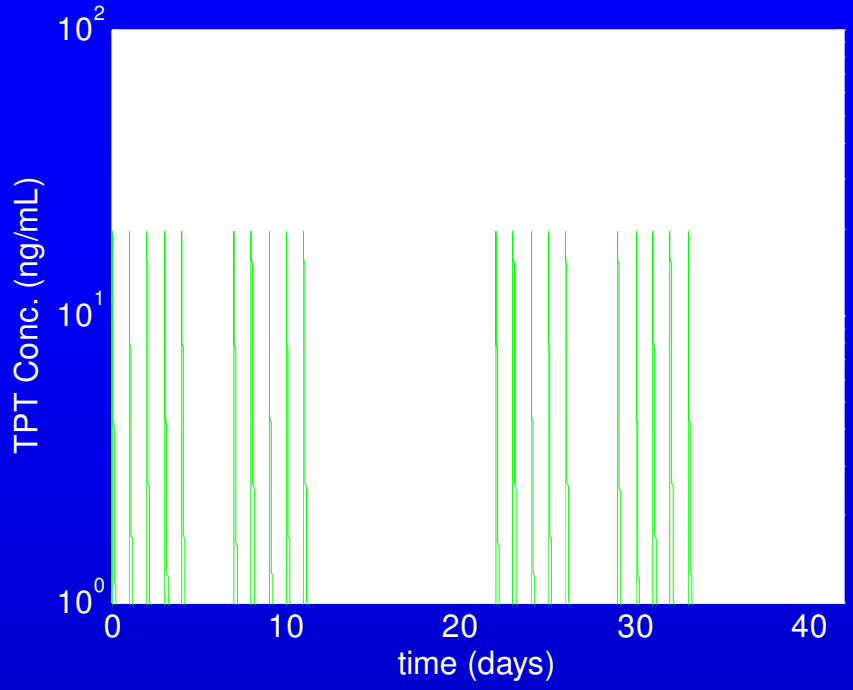


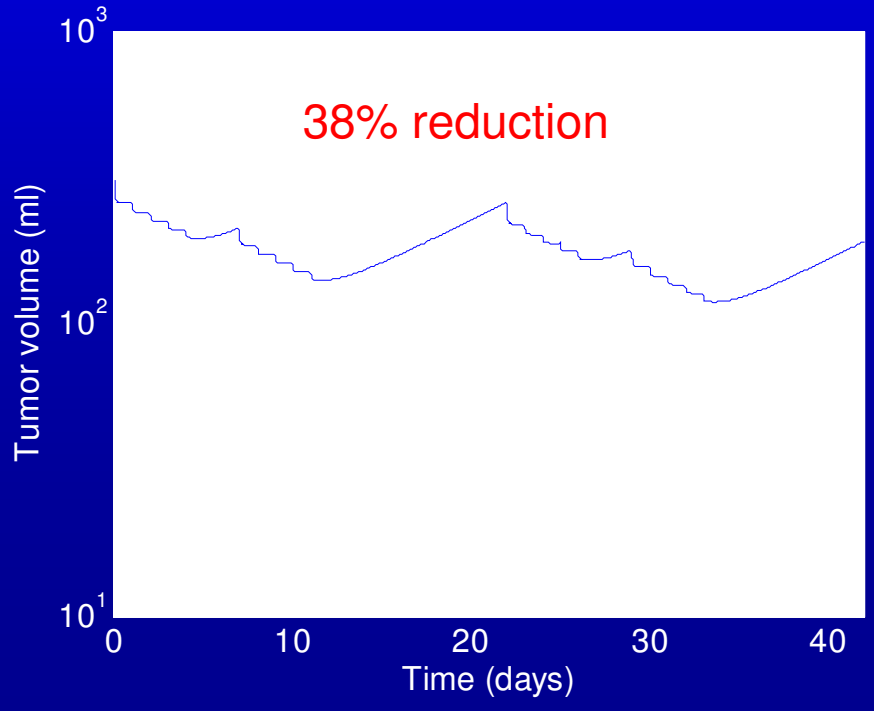



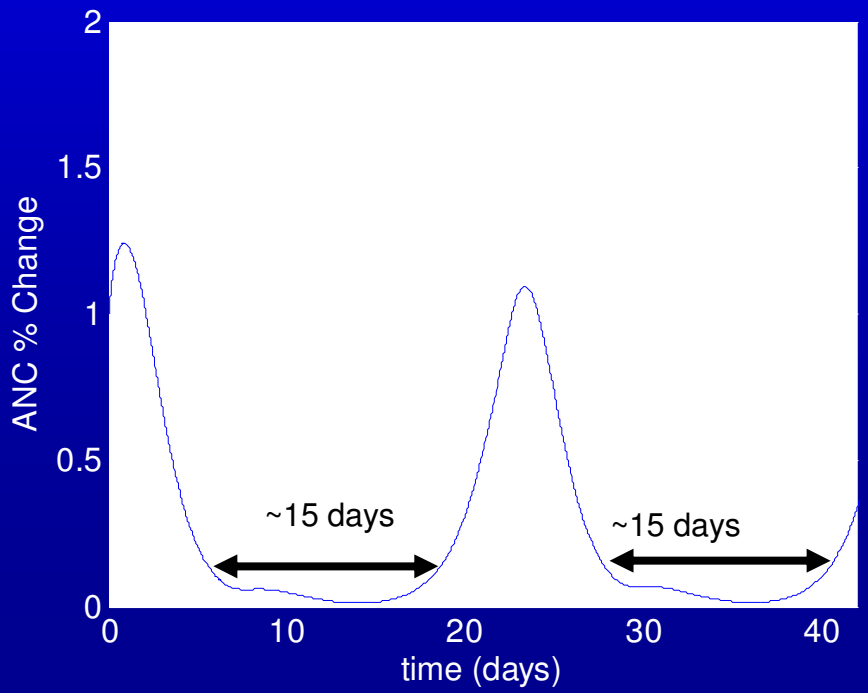



# Results

- Current dosing schedule w/o G-CSF:
  - TPT 1 mg/m$^2$/day daily×5×2
  - Note: Lower dose due to toxicity
  - Full dose would have delayed treatment ~8 days.

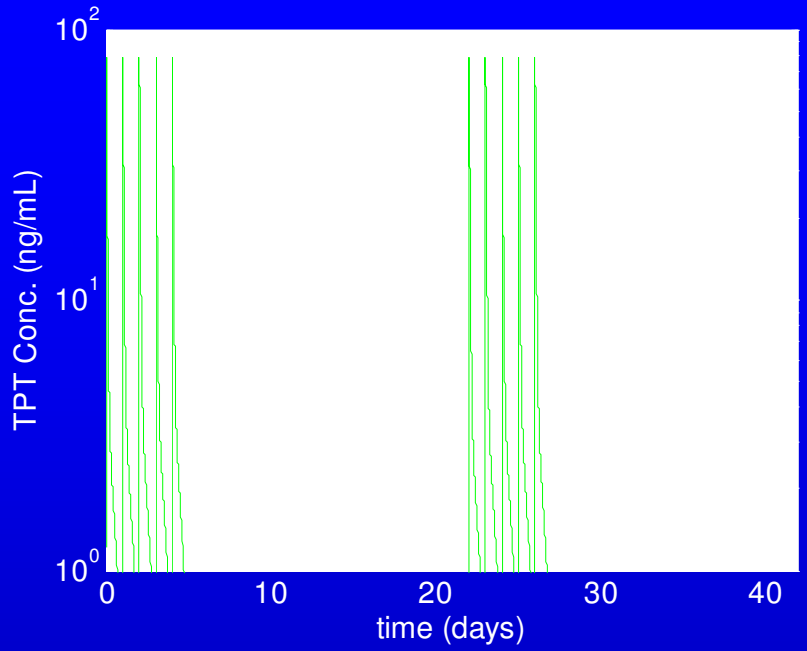


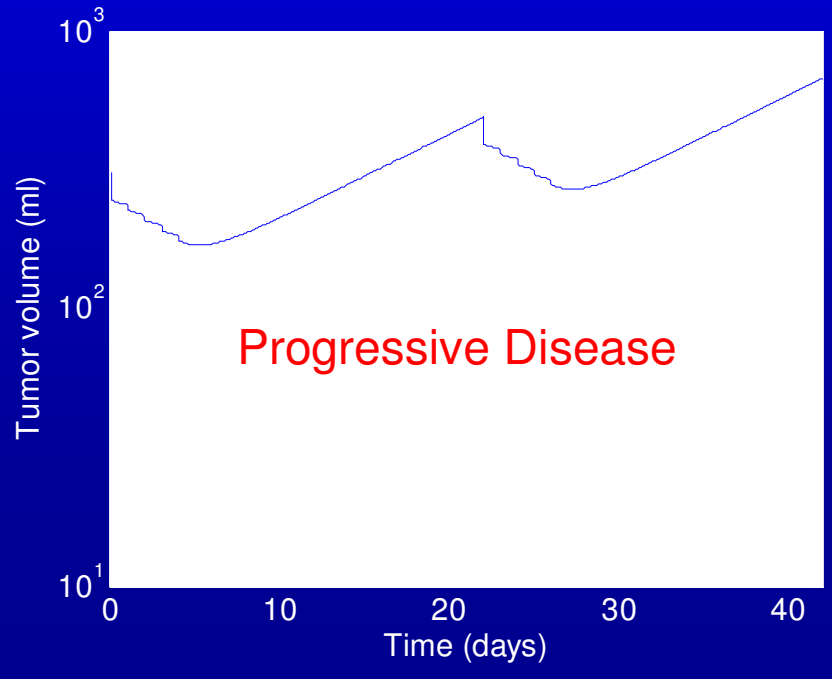



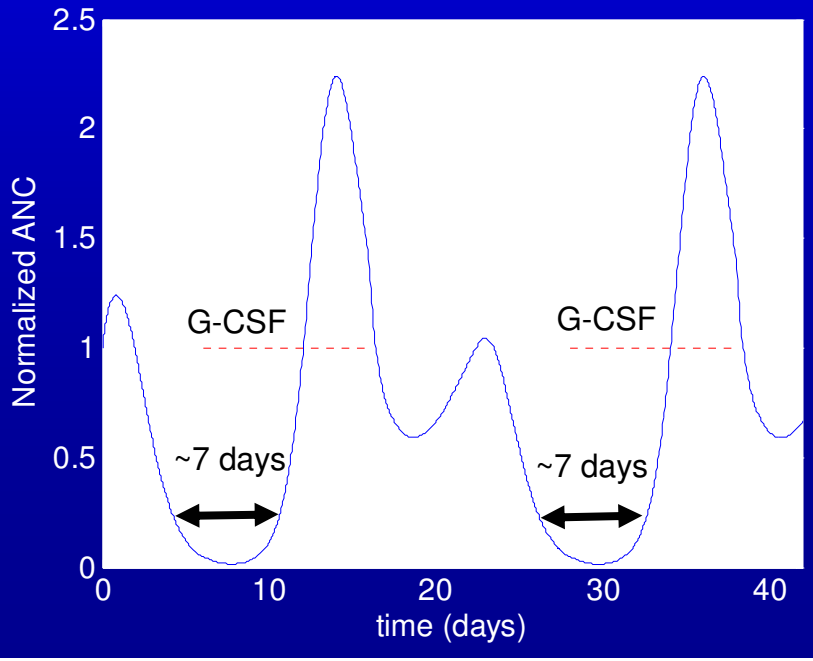



# Results

- Shorter dosing schedule:
  - TPT 4 mg/m$^2$/day daily×5
    - NOTE: 2 × previous simulation
    - ↑ doses **don't** improve results due to CCS nature of TPT
  - G-CSF 5 mg/kg/day daily day 6 to 16
  - Less myelosuppression suggests <u>decreasing</u> time between courses



# Comments and Conclusions

- Preliminary modeling and simulation results relate well to known clinical results
- Current model allows for comparison of treatment strategies *in silico*
- Optimal control techniques can automate determining the *best* treatment dose/schedule based on the model assumptions.
- Consider various cell-kill hypotheses.
  - **Skipper's log-kill model:** Proportional to sensitive population (Schabel, Skipper, and Wilcox, CCR 1964)
  - **Norton Simon Hypothesis**: Proportional to the growth rate (Norton and Simon CTR 1977, 1986)