

Using Mathematical Modeling to Tailor the Delivery of G-CSF in Disease States

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OUTLINE

Cyclical Neutropenia (CN)

Mathematical Modeling of CN

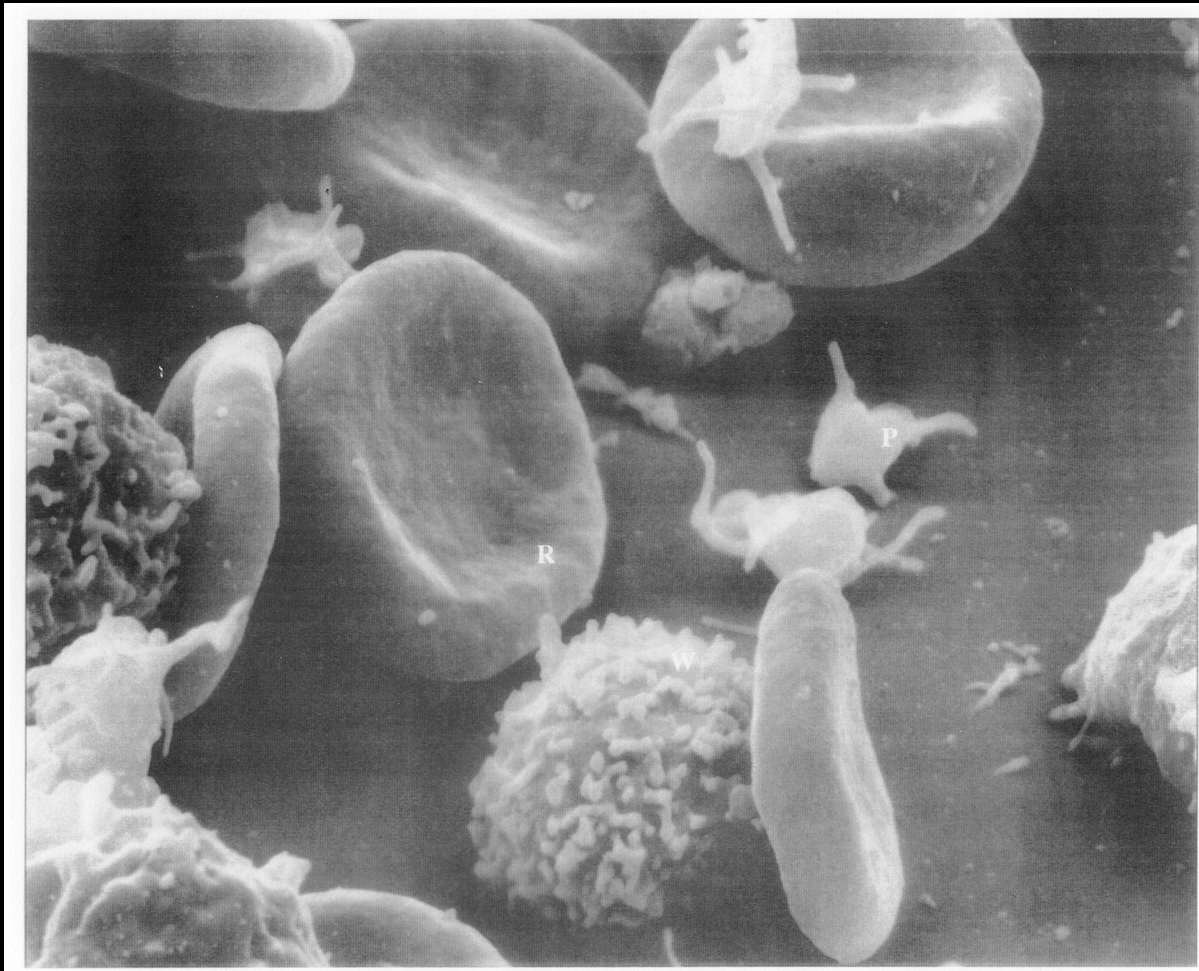
Simulations of G-CSF effects in CN: Timing
& Dose

G-CSF and Chemotherapy

Optimal treatment with G-CSF

Conclusions

Three major types of blood cells

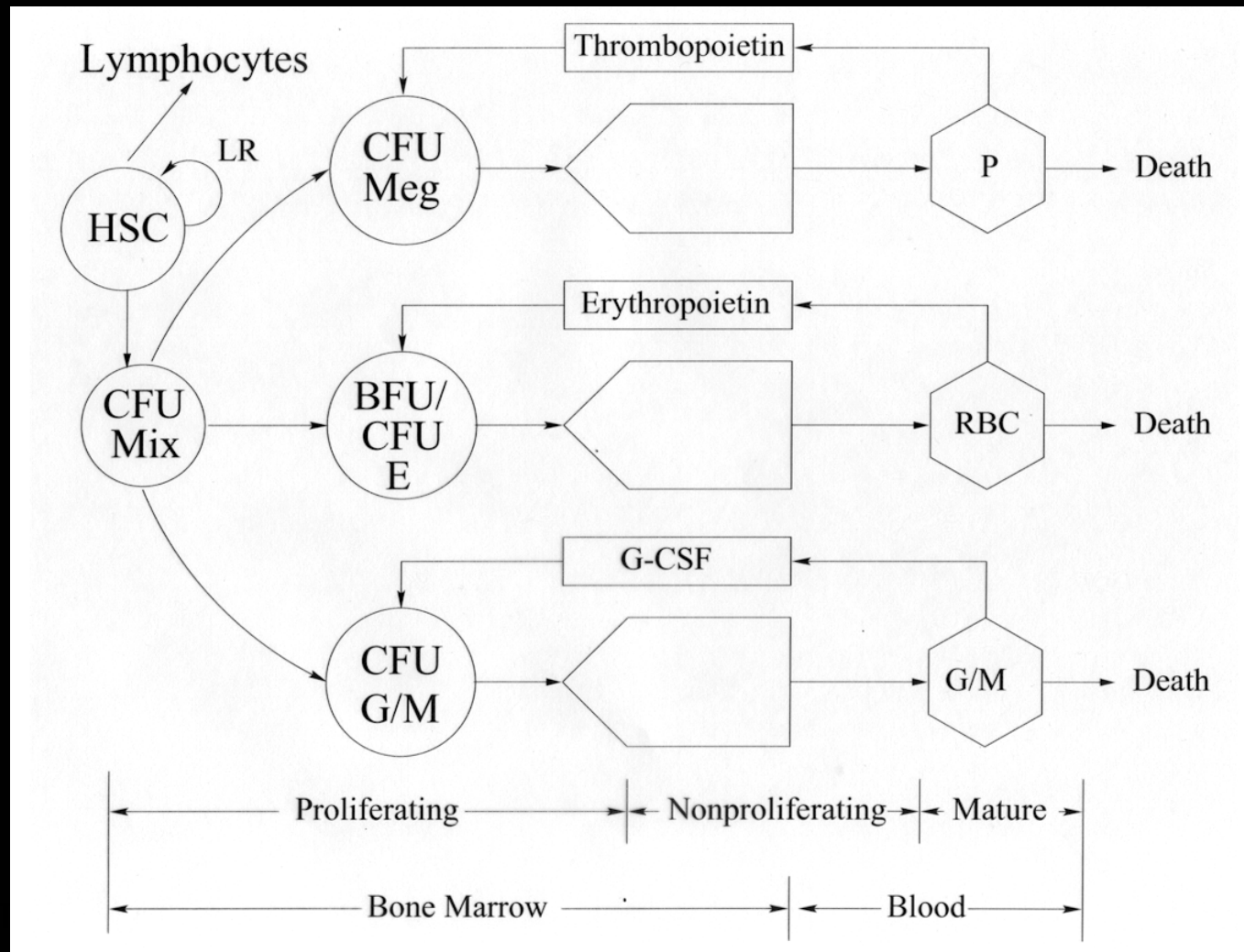


Lifetime production: Humans

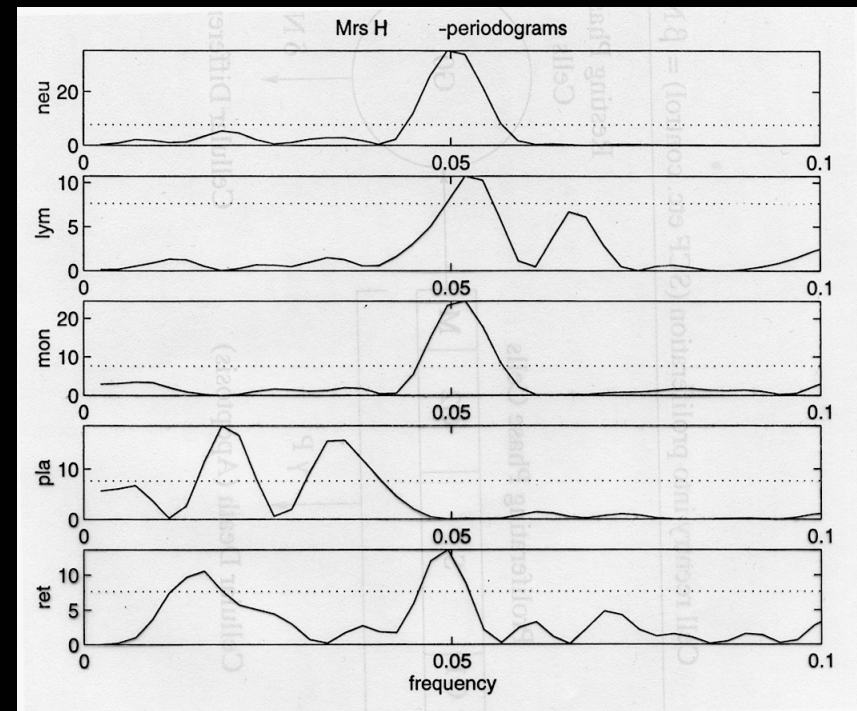
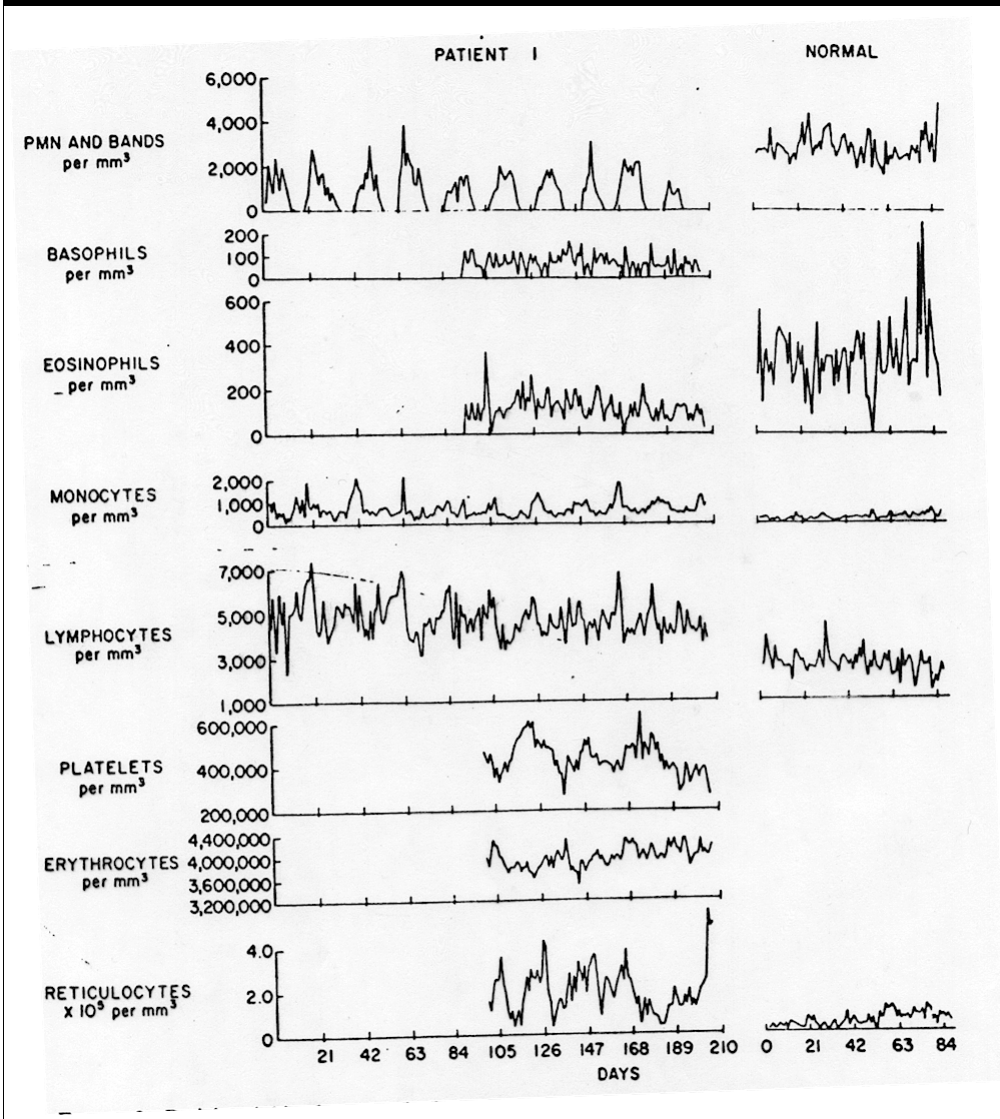
- 500 kg RBC
- 160 kg WBC
- 30 kg Platelets

Hematopoietic
production equivalent
to our body weight
every 10 years

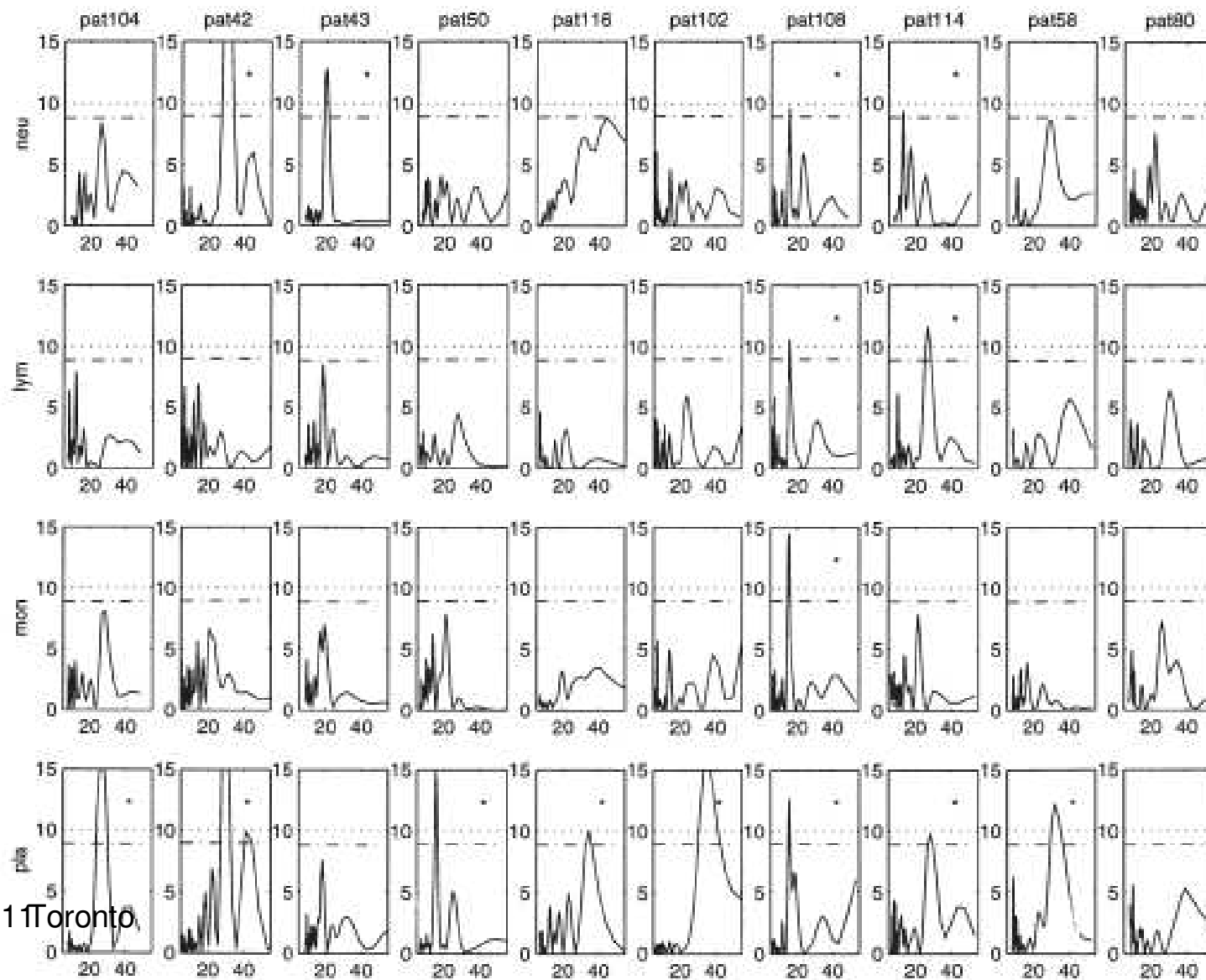
Hematopoietic Control



Cyclical Neutropenia: Mrs. H



Oscillations in neutropenics



Characteristics of CN

Period between 11 and 52 days

Typically involves more than one cell line

Neutrophil levels: Normal to almost zero

High level of apoptotic figures: bone marrow

Interruption: promyelocyte-myelocyte stage

Mutation in ELA2 gene

Mutant neutrophil elastase somehow triggers
apoptosis

Treatment with G-CSF

G-CSF decreases period to between 11 and 14 days or stops cycling

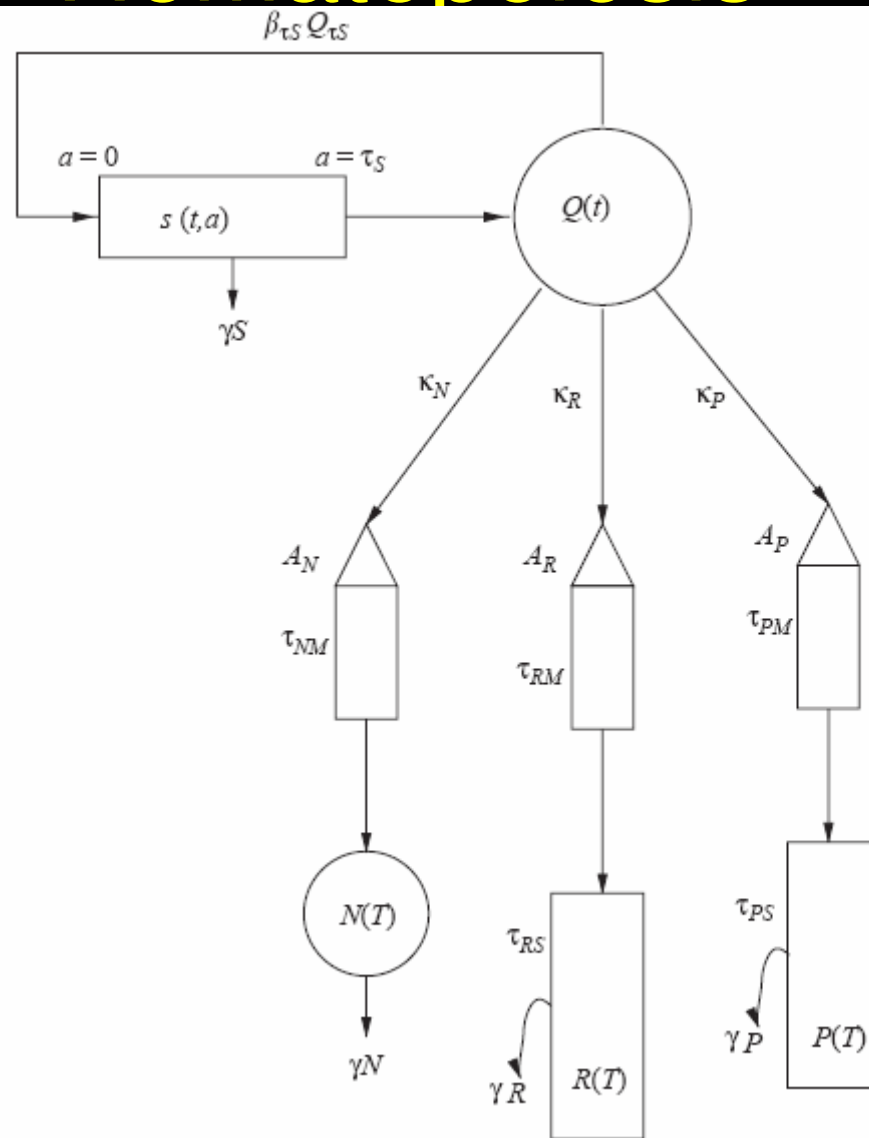
Increases amplitude of oscillation

Increases nadir (important)

G-CSF known to interfere with apoptosis

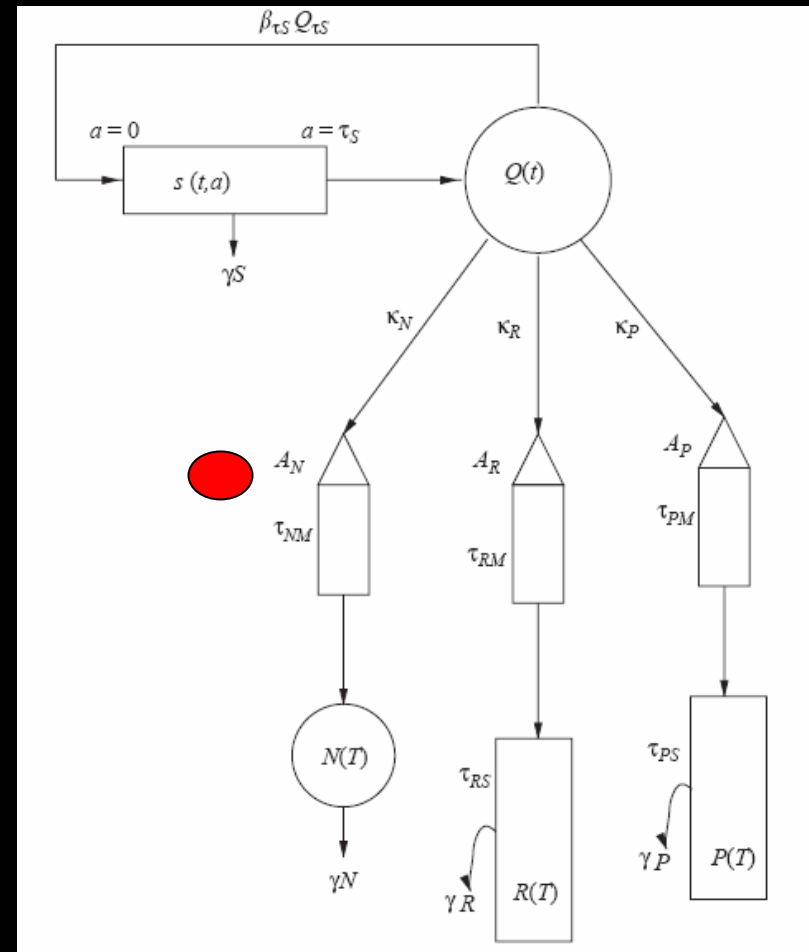
Treatment is expensive: ca. \$200/time

Mathematical Model Hematopoiesis



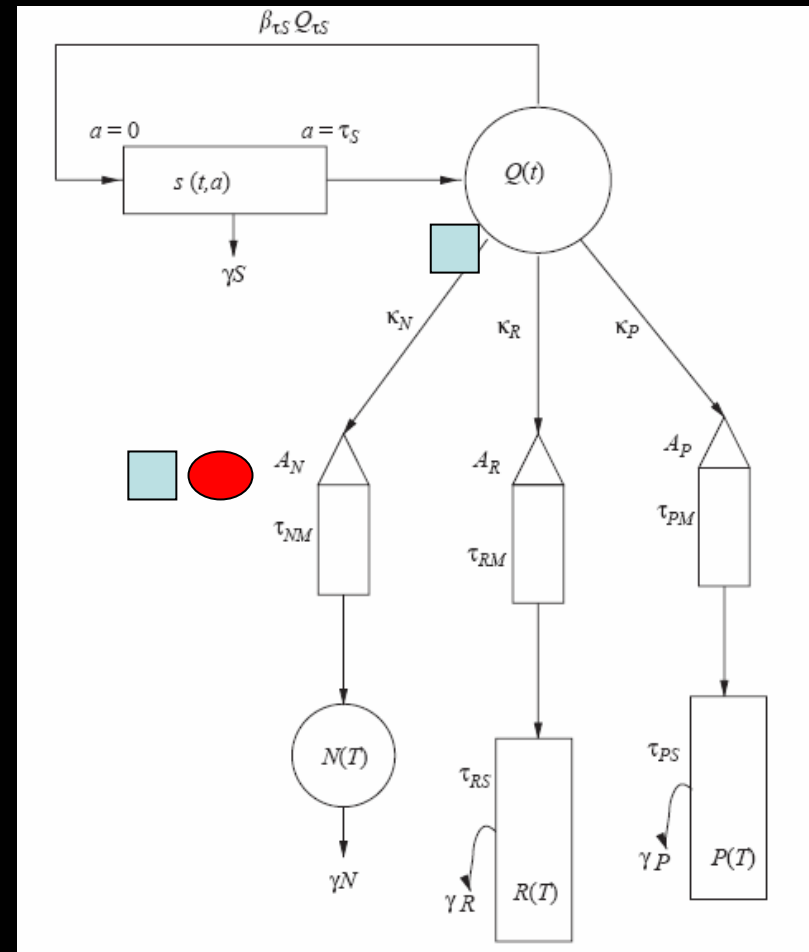
J. theor. Biol. (2005) 237, 133

- Large comprehensive model
- To fit clinical CN data
- Parameter changes in apoptosis & HSC reentry



J. theor. Biol. (2005) 237, 133

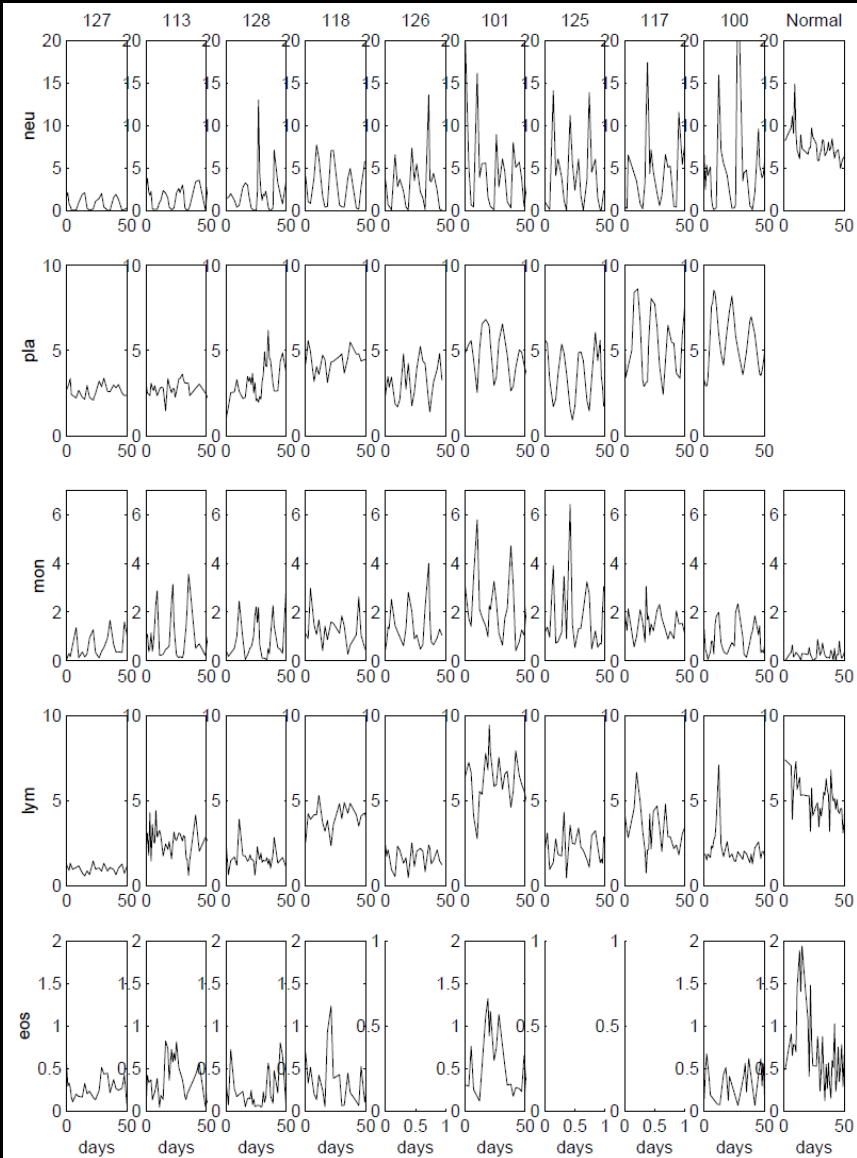
- Large comprehensive model
- To fit clinical CN data
- Parameter changes in apoptosis & HSC reentry
- G-CSF affects apoptosis & differentiation



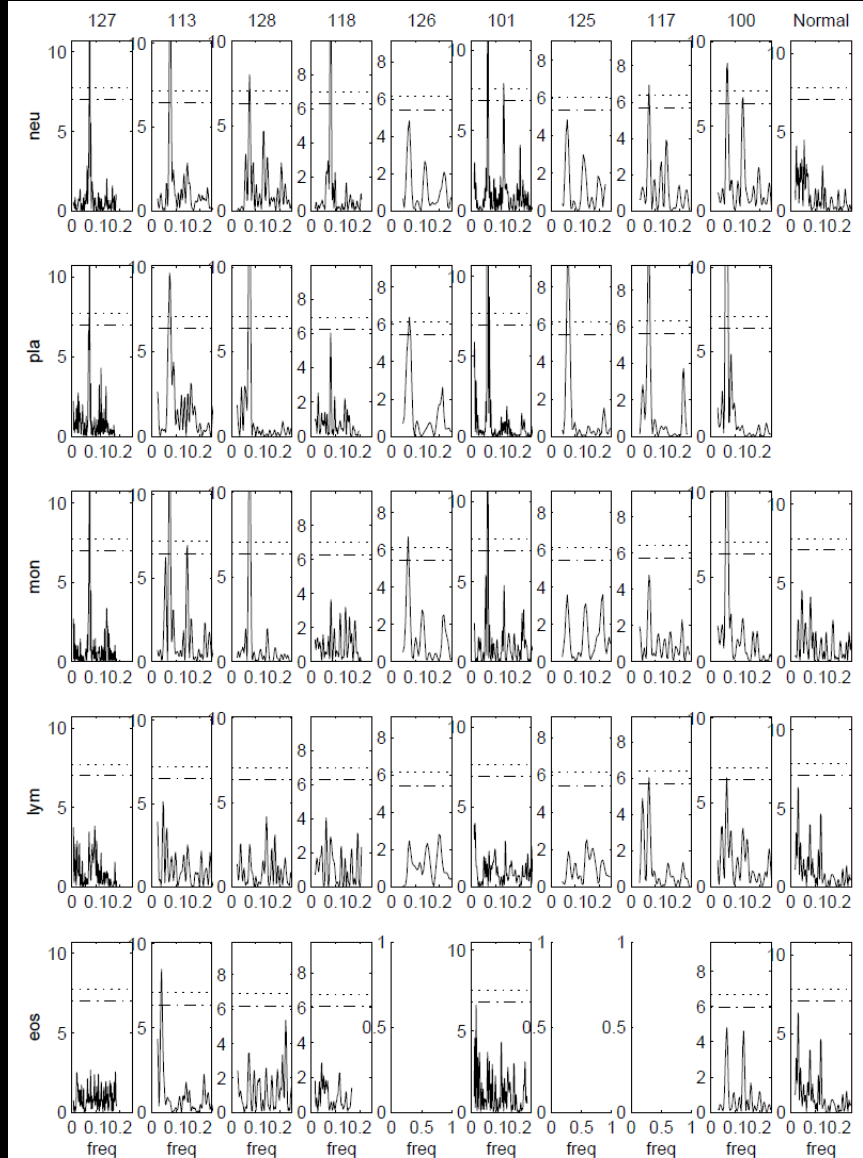
Grey collies & CN



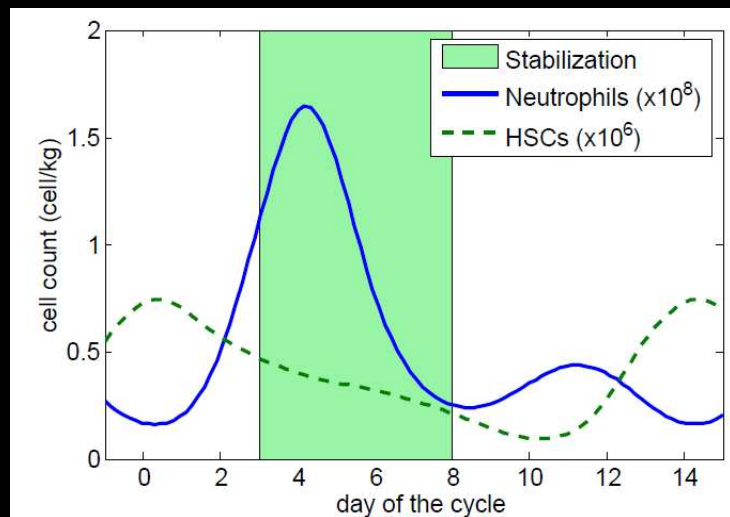
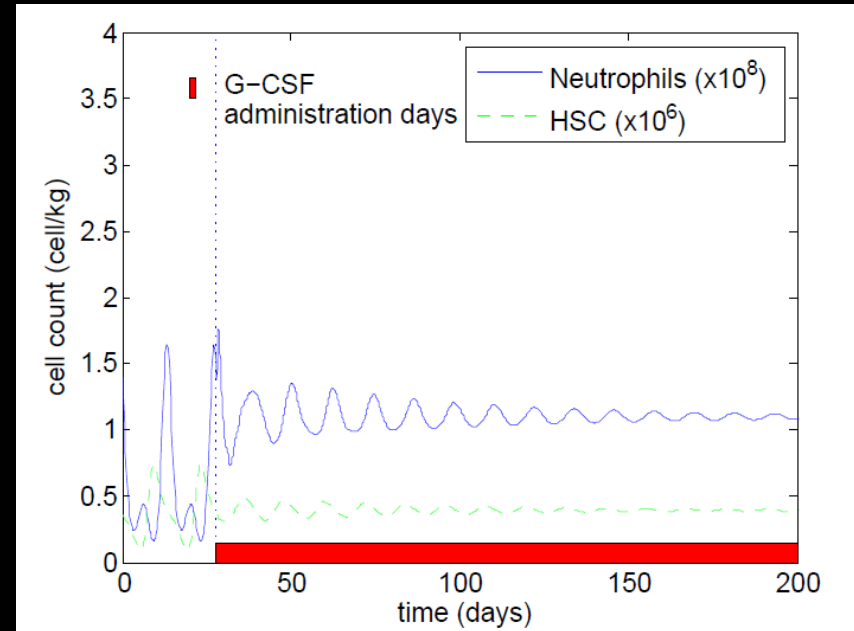
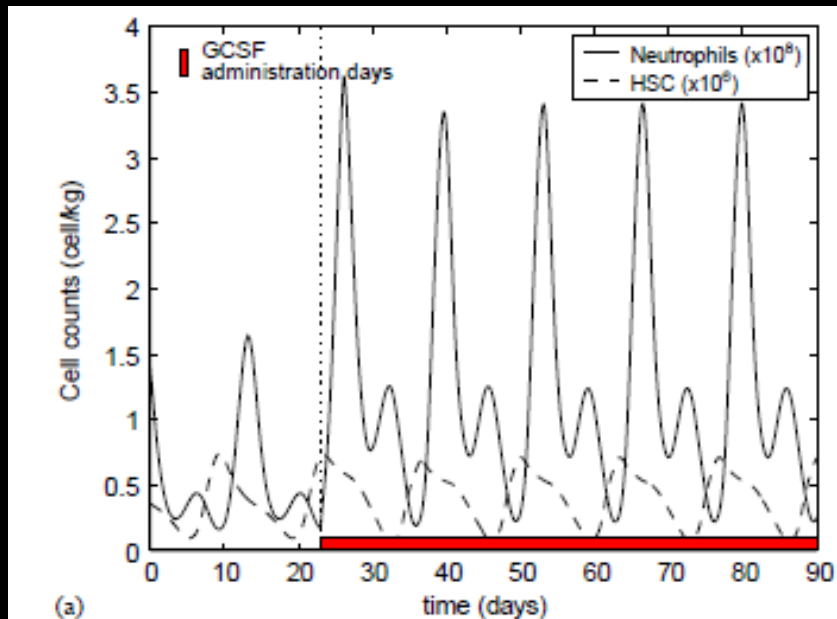
Data



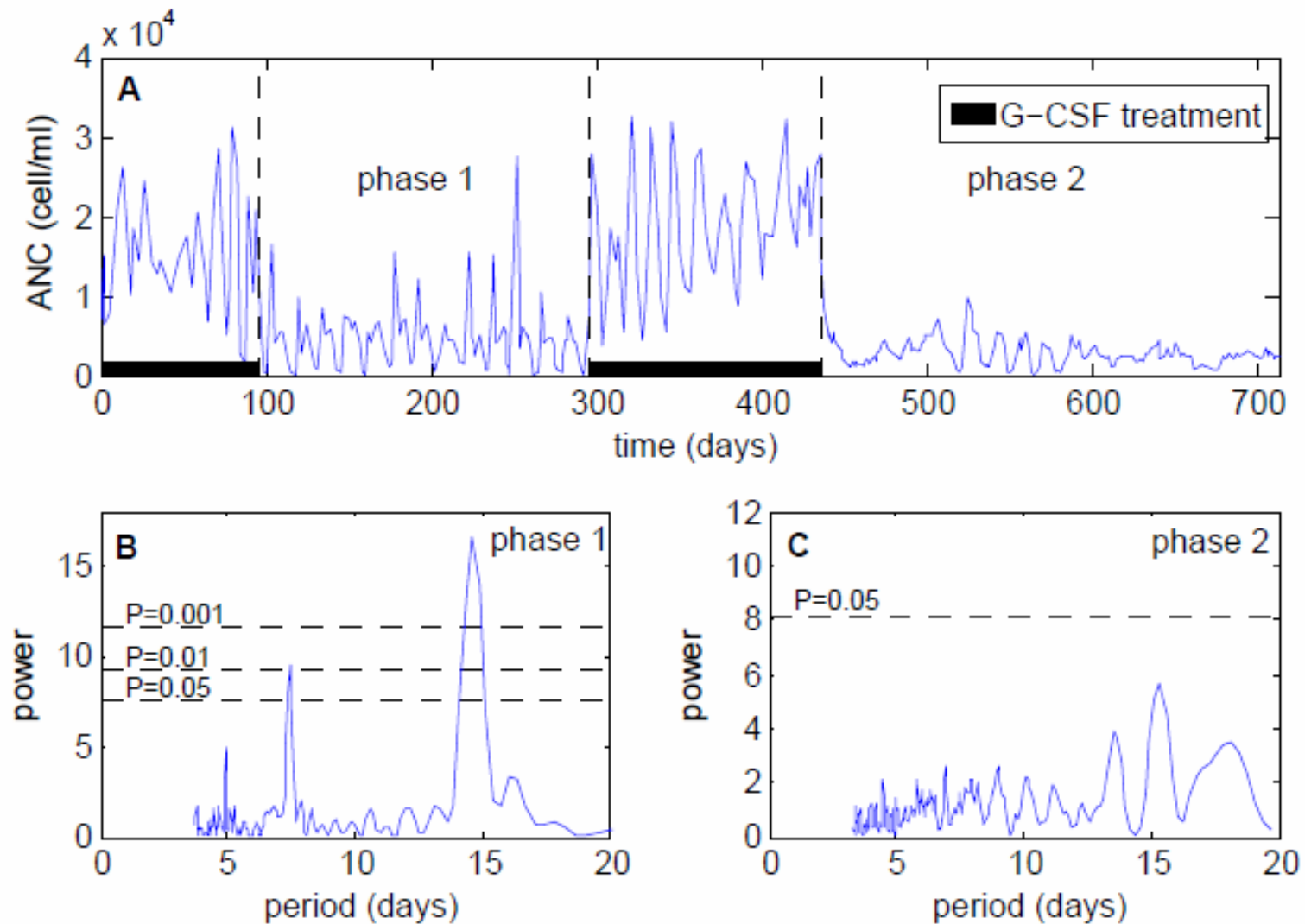
Periodograms



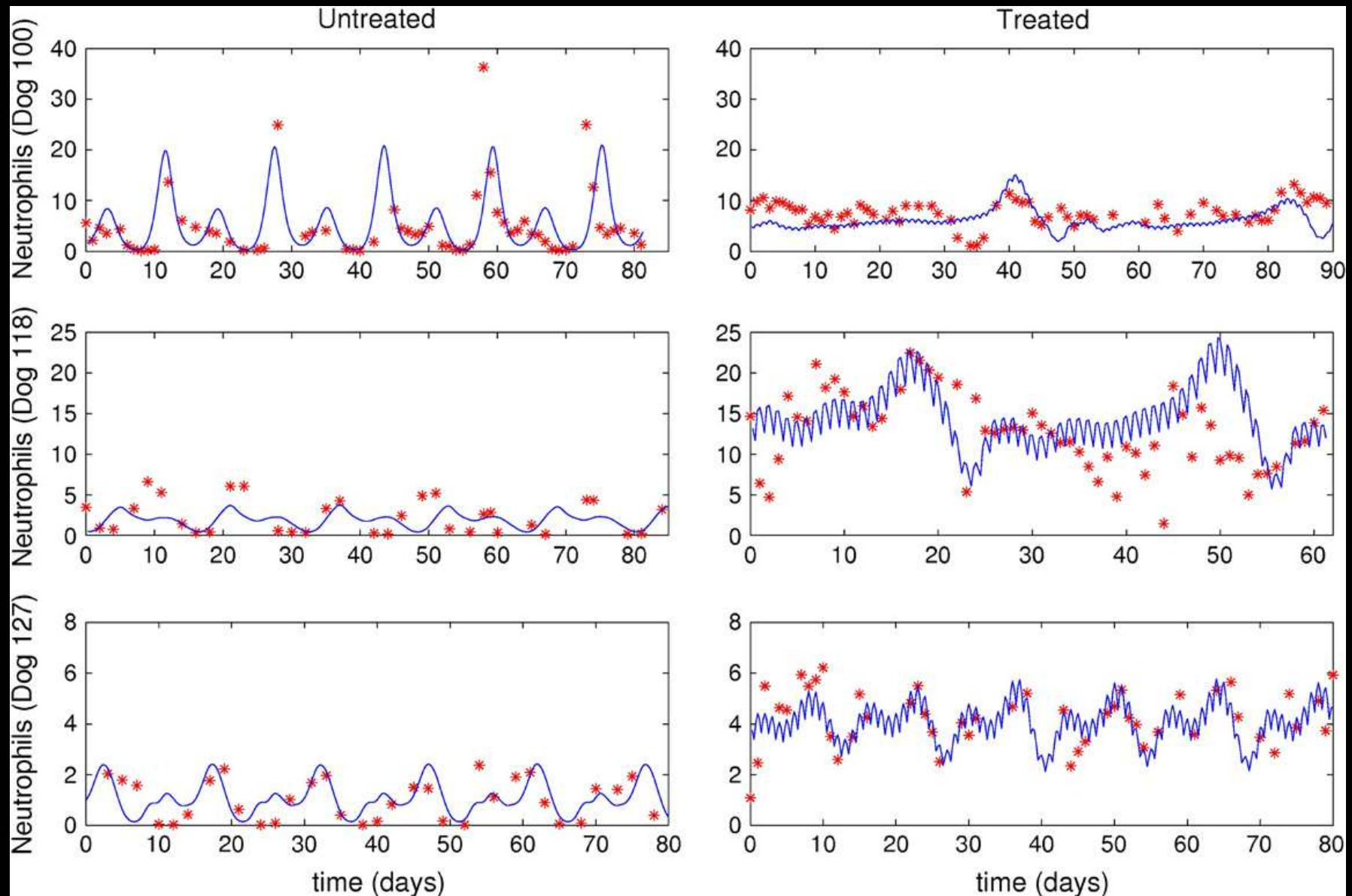
Daily G-CSF: start day & dynamics



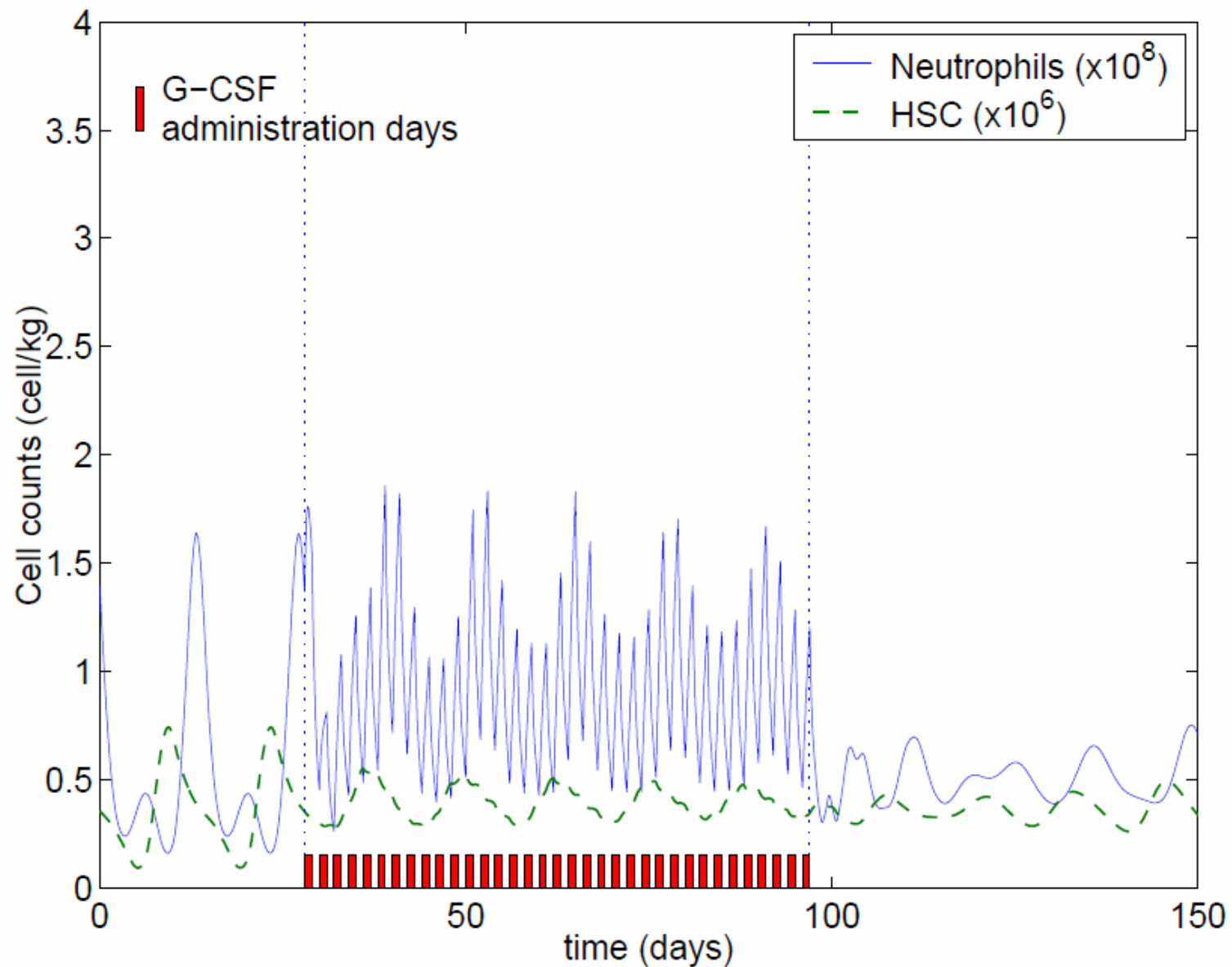
Experimental verification: Oprah



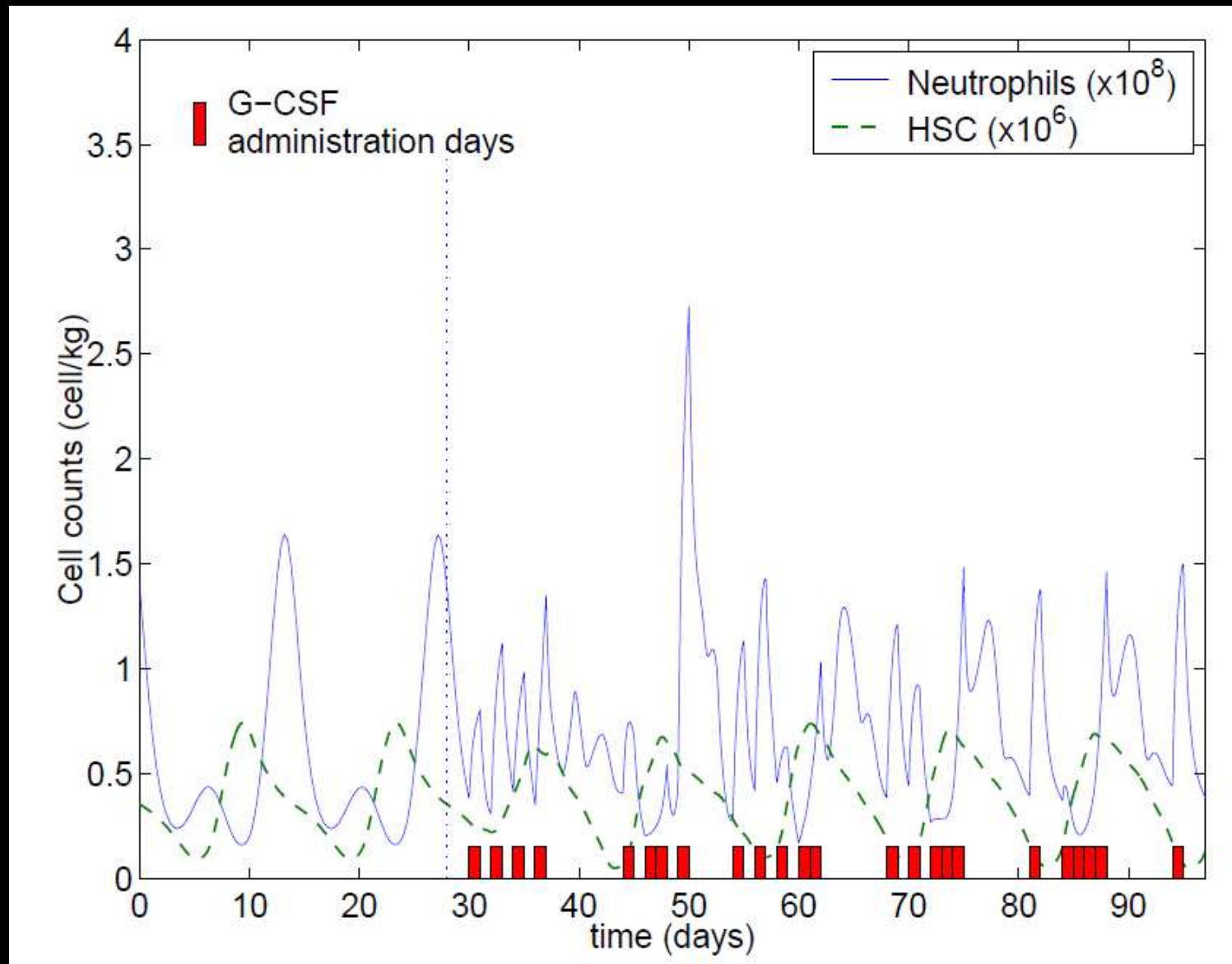
Data from 3 dogs: Daily G-CSF



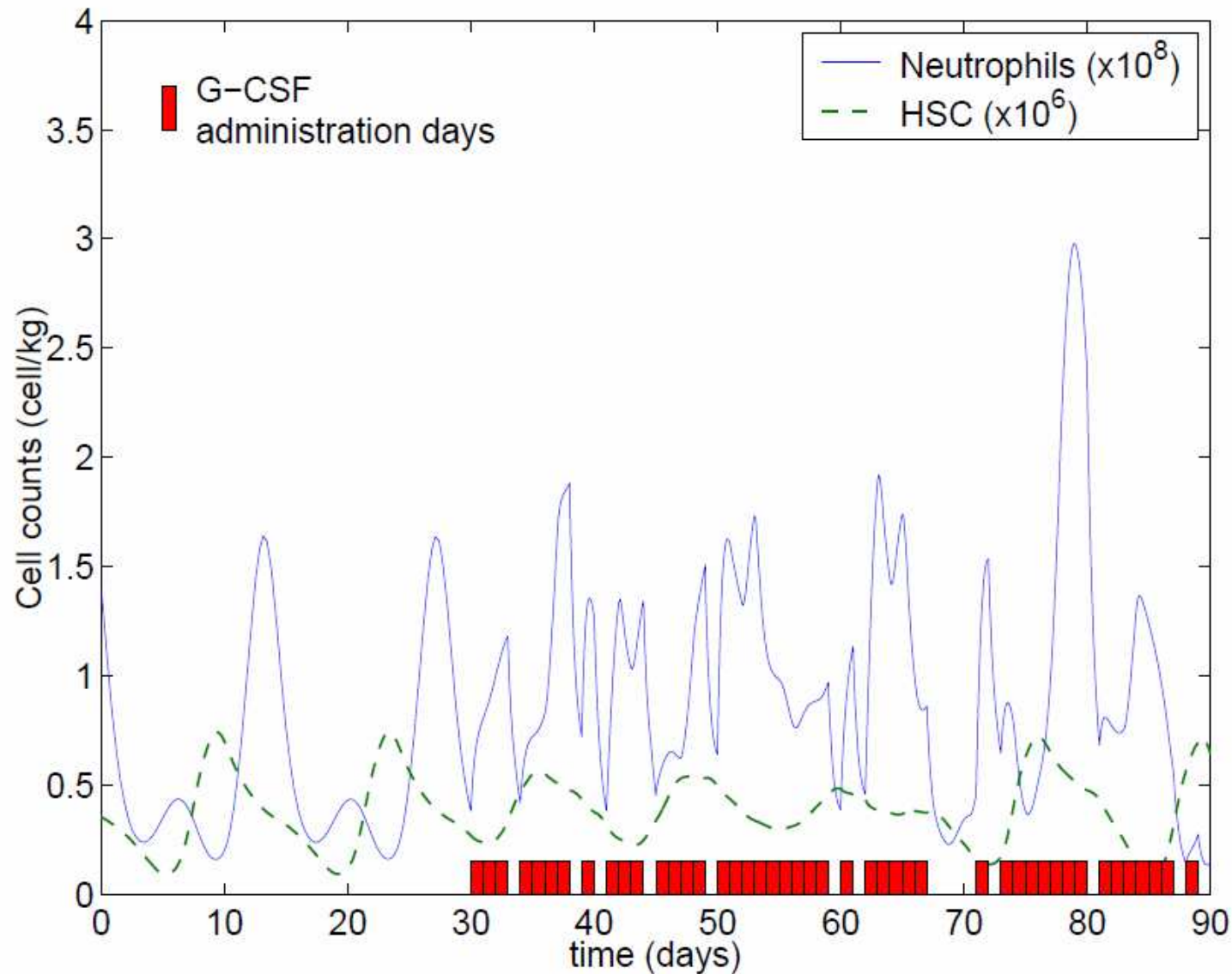
Alternate day G-CSF



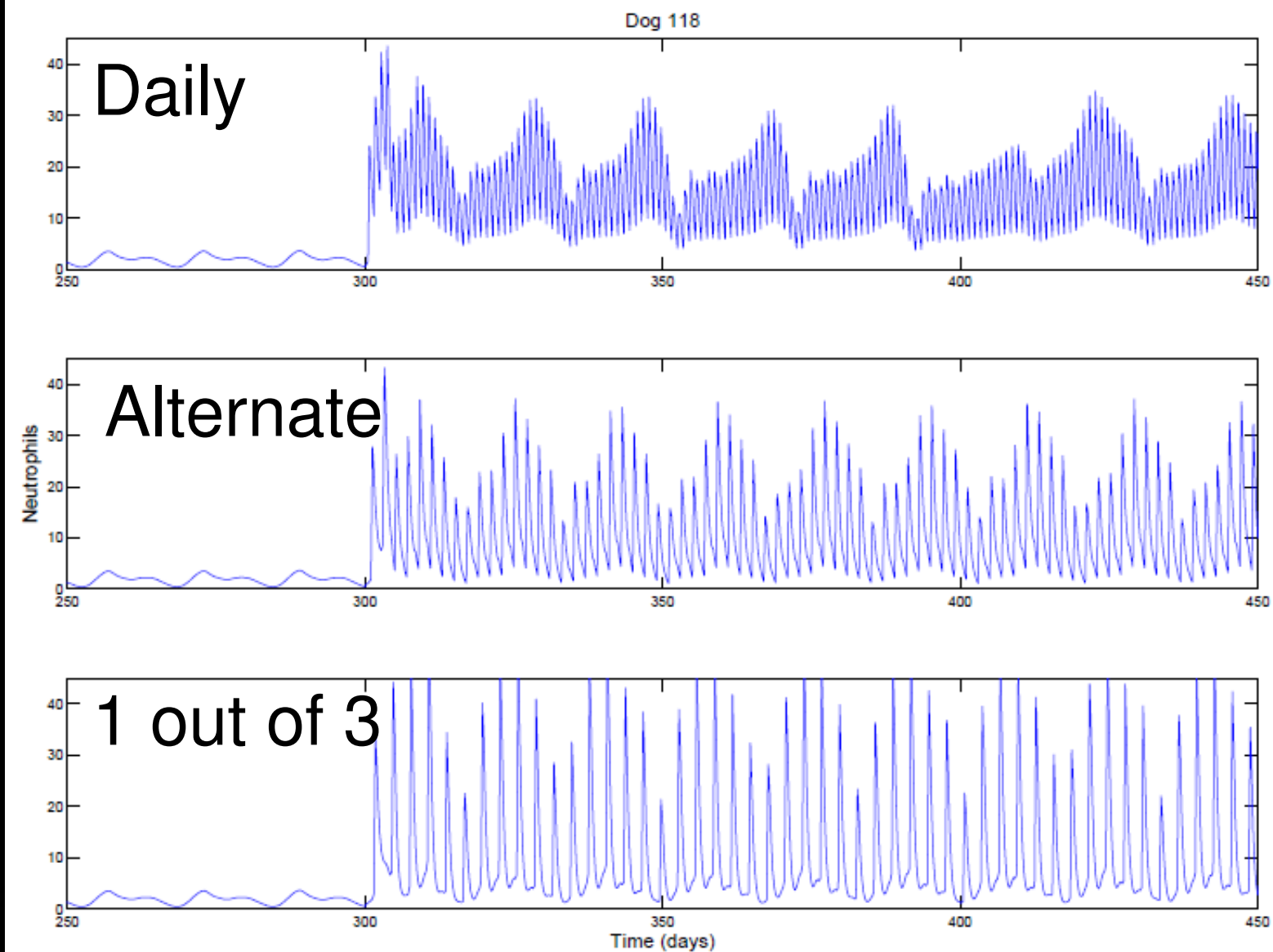
Threshold dependent protocol



Random protocol (70%)



Grey collie 118: three protocols



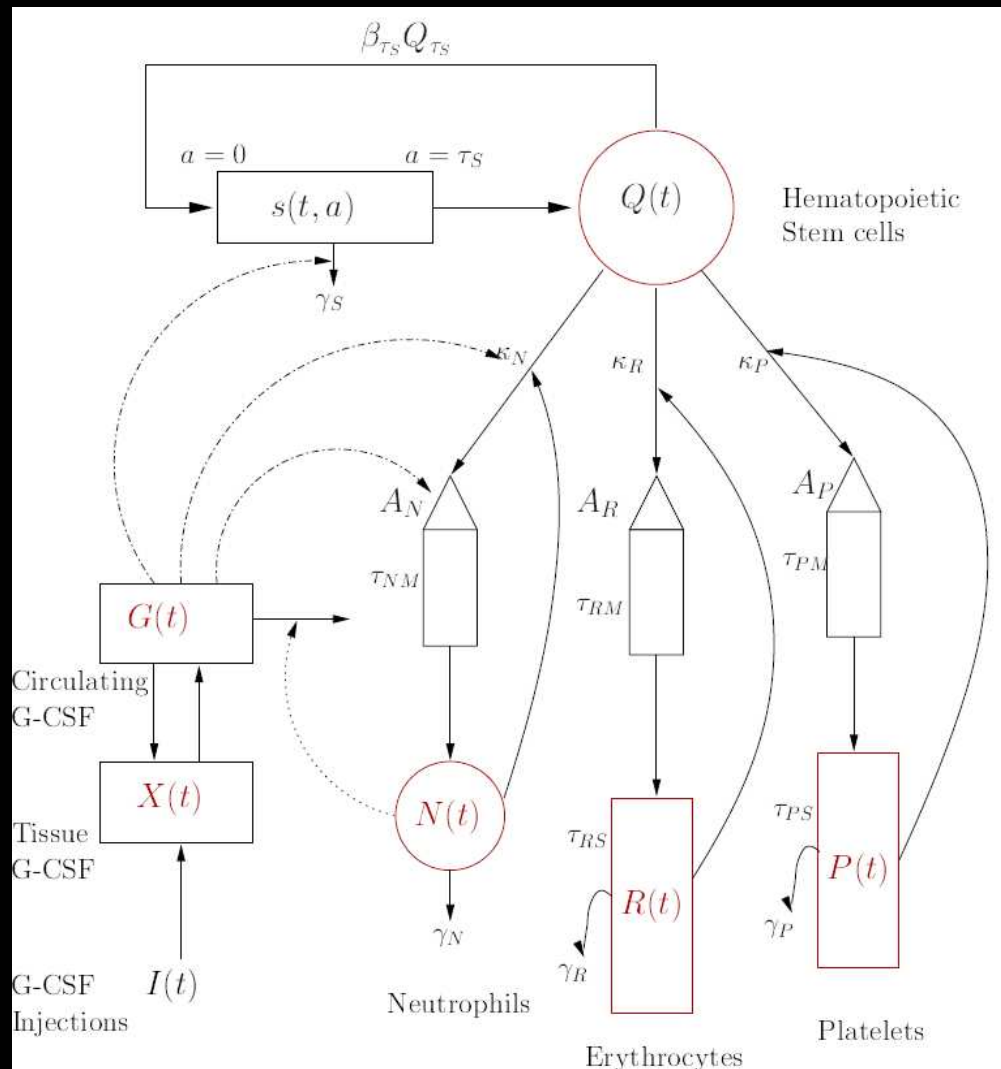
G-CSF & Cyclical Neutropenia

Timing of treatment start has profound effect on outcome

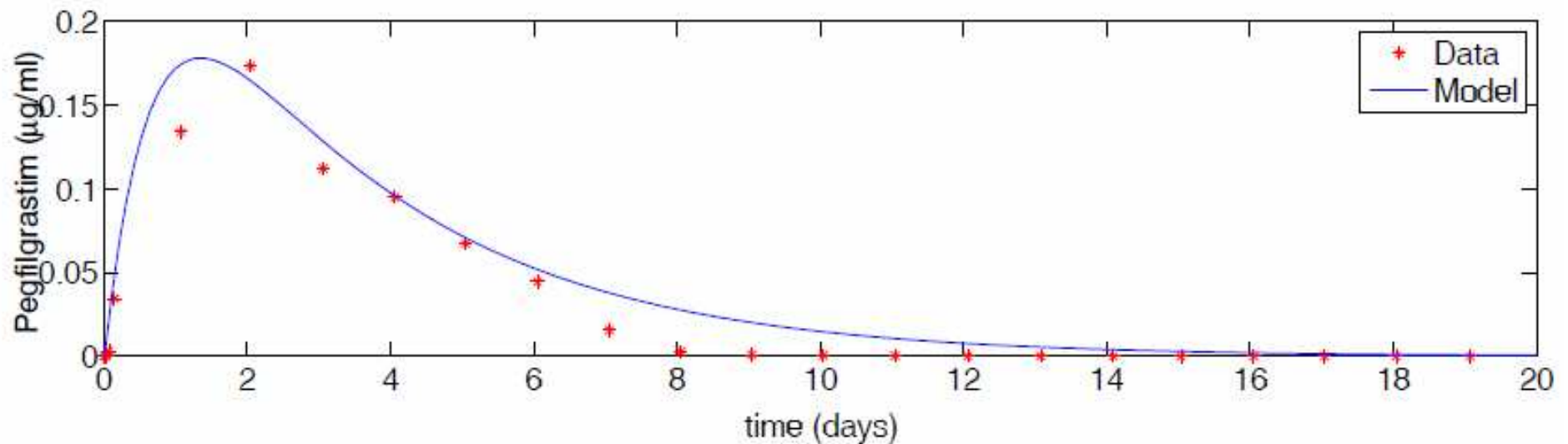
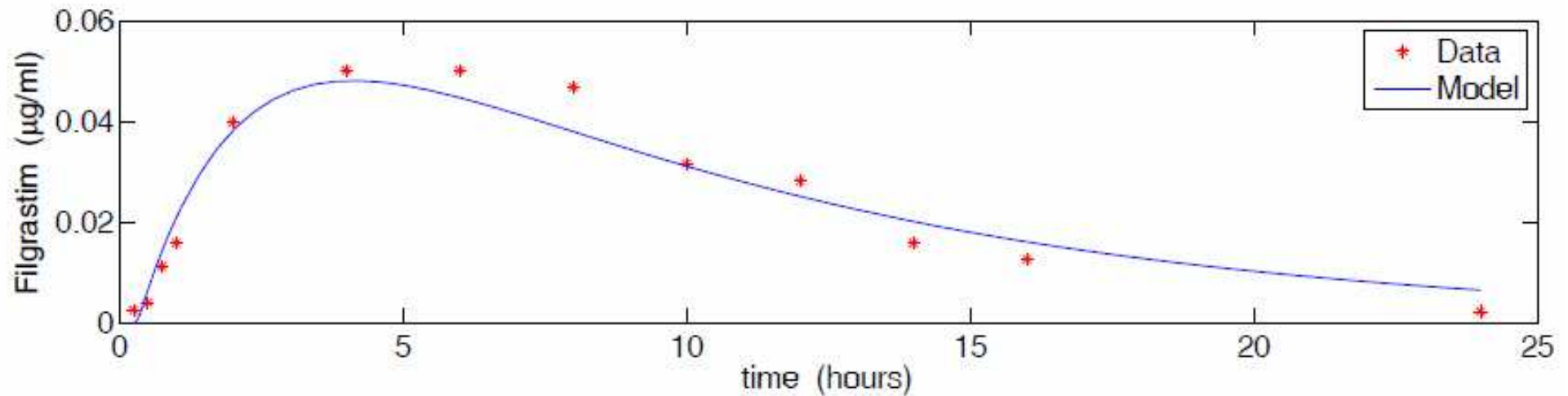
Alternate day treatment and other protocols: effective as daily

All result in significant decrease in amount of G-CSF needed and savings

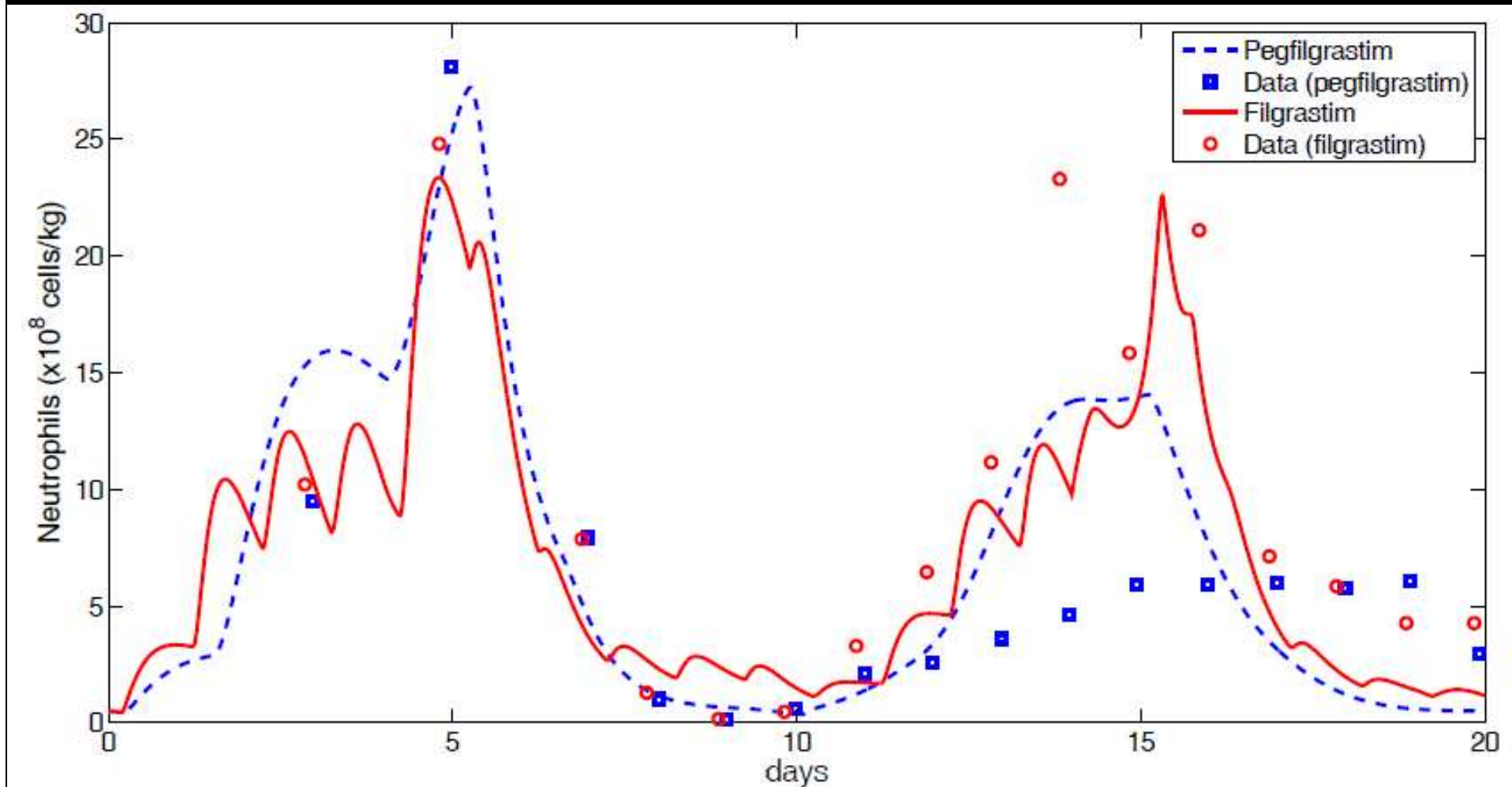
G-CSF following chemotherapy



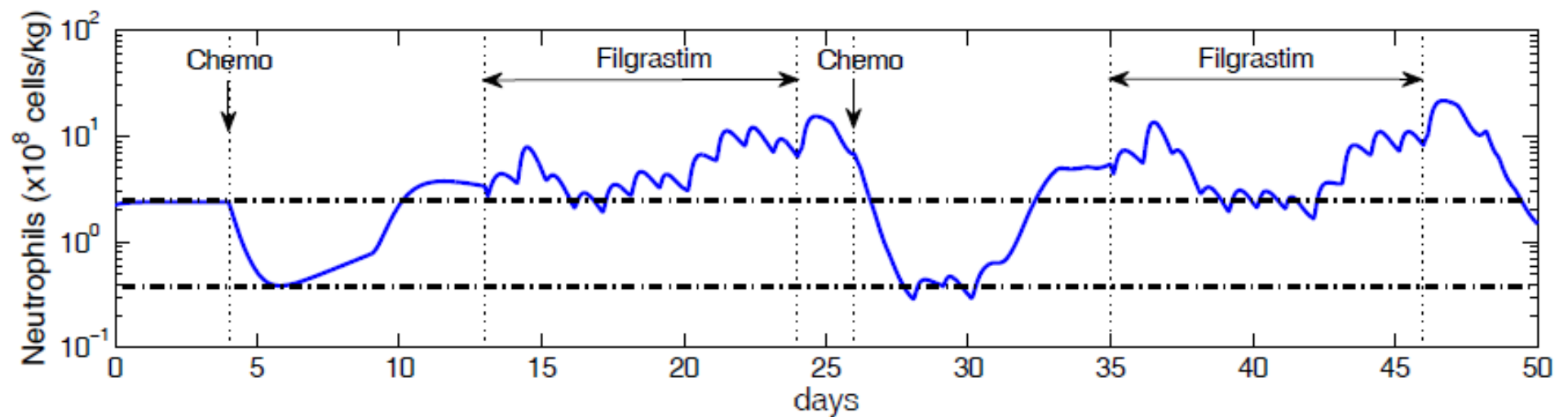
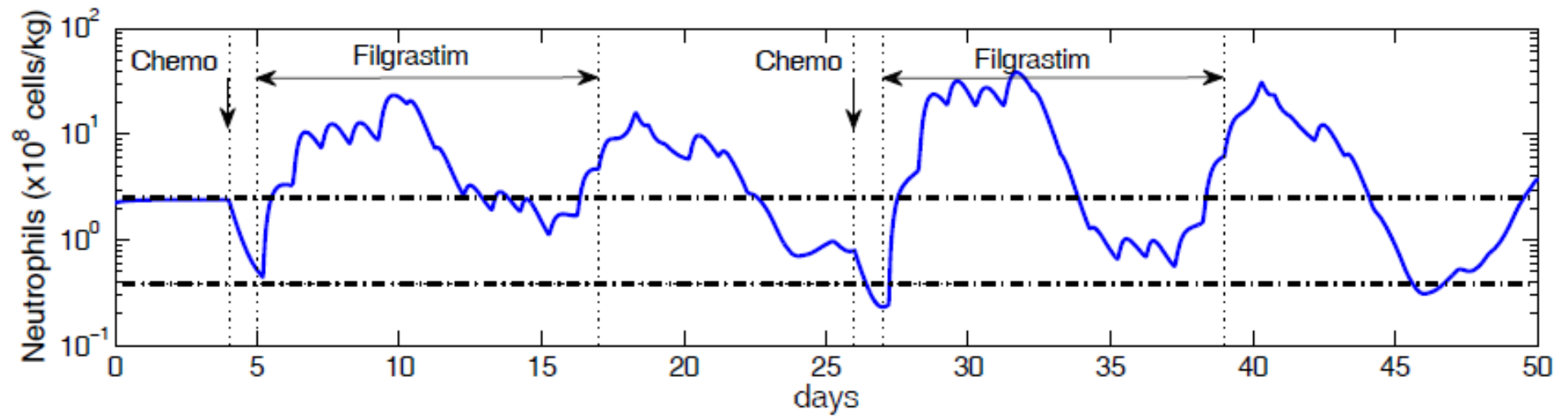
Single bolus injection: Data vs. model



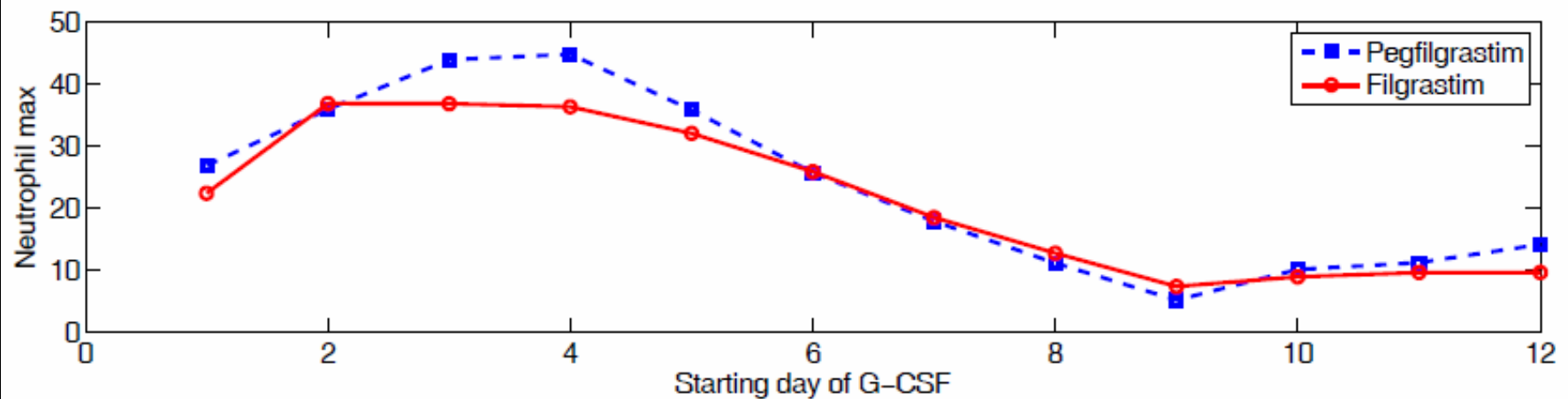
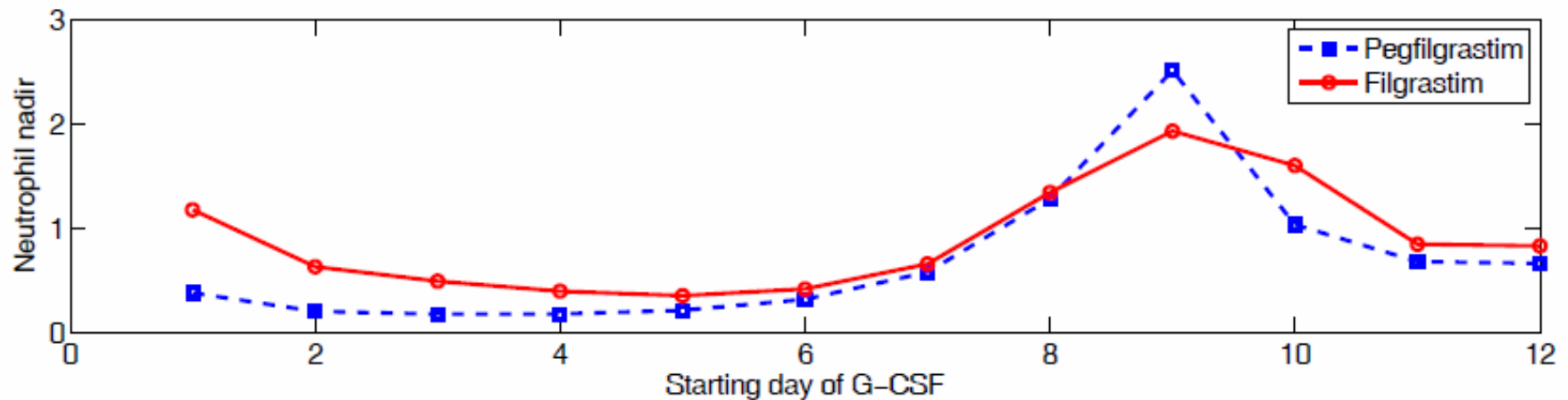
Daily G-CSF: Data vs. model



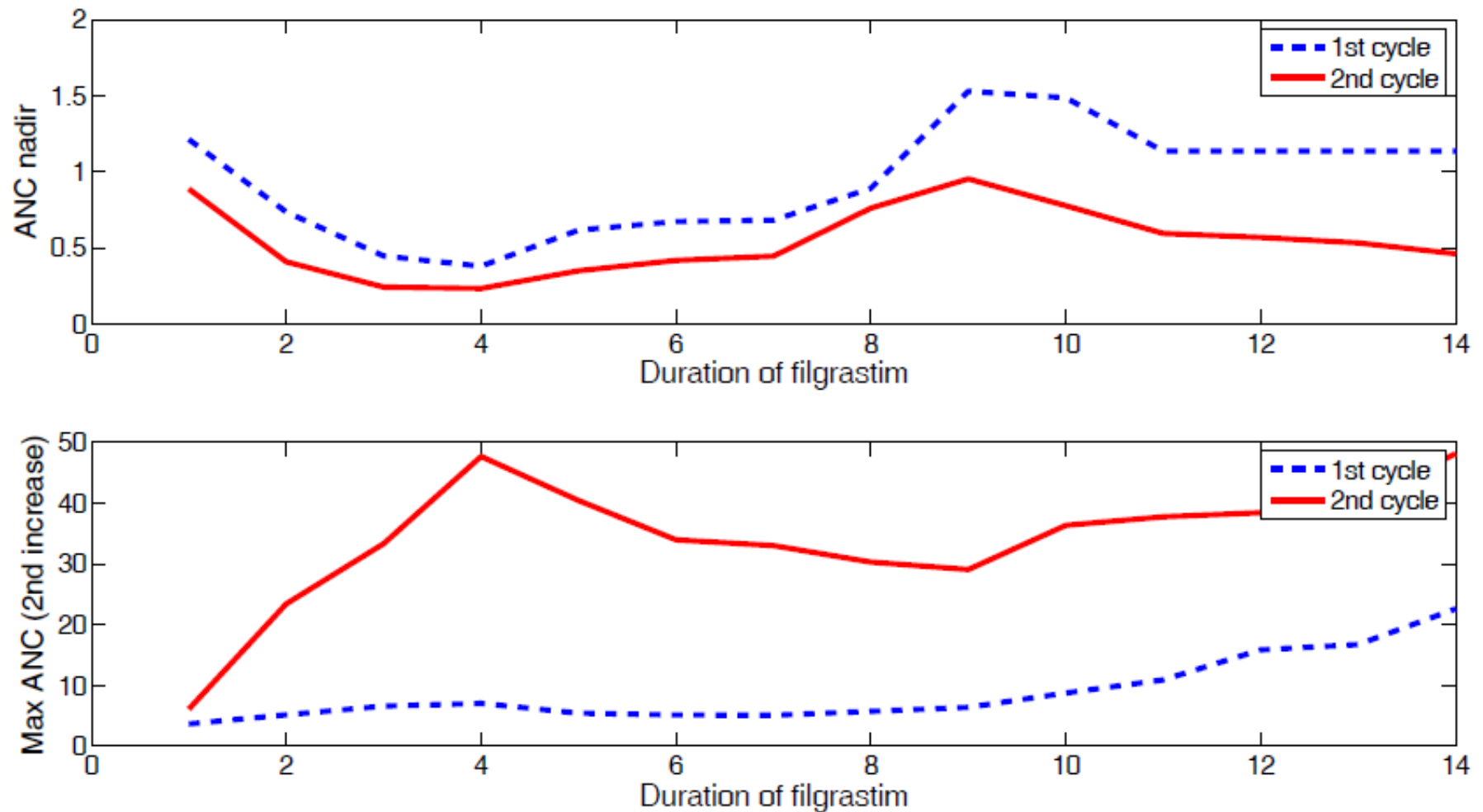
11 day course of Filgrastim



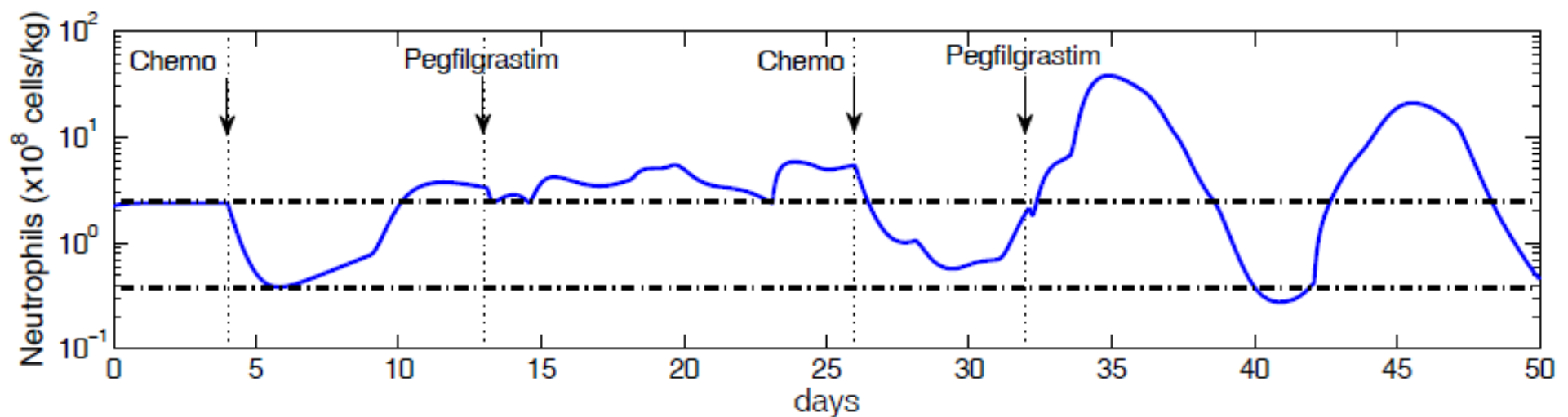
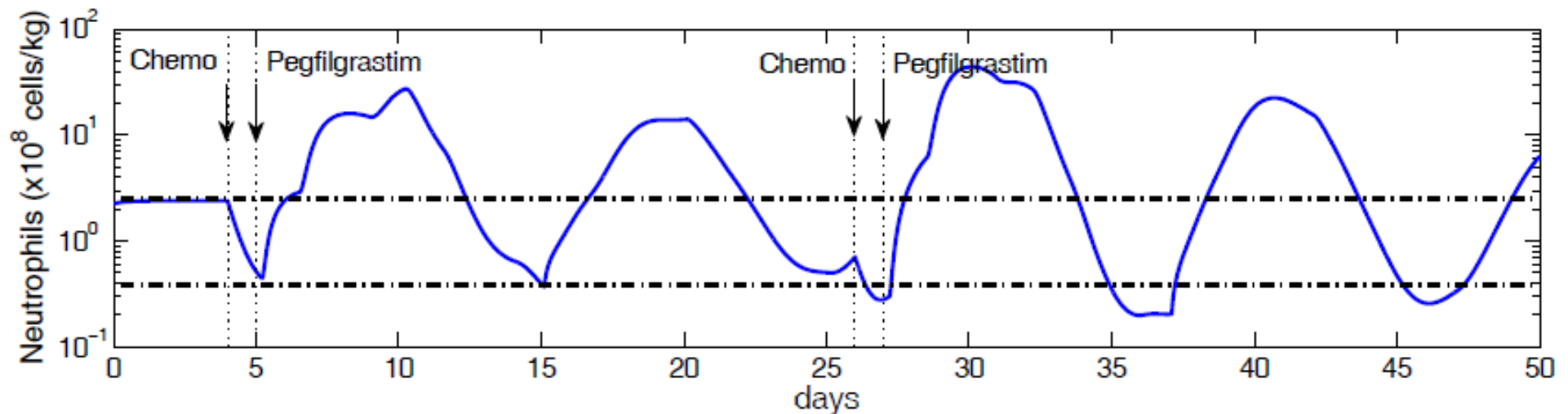
Pegfilgrastim & Filgrastim: Effect of starting day



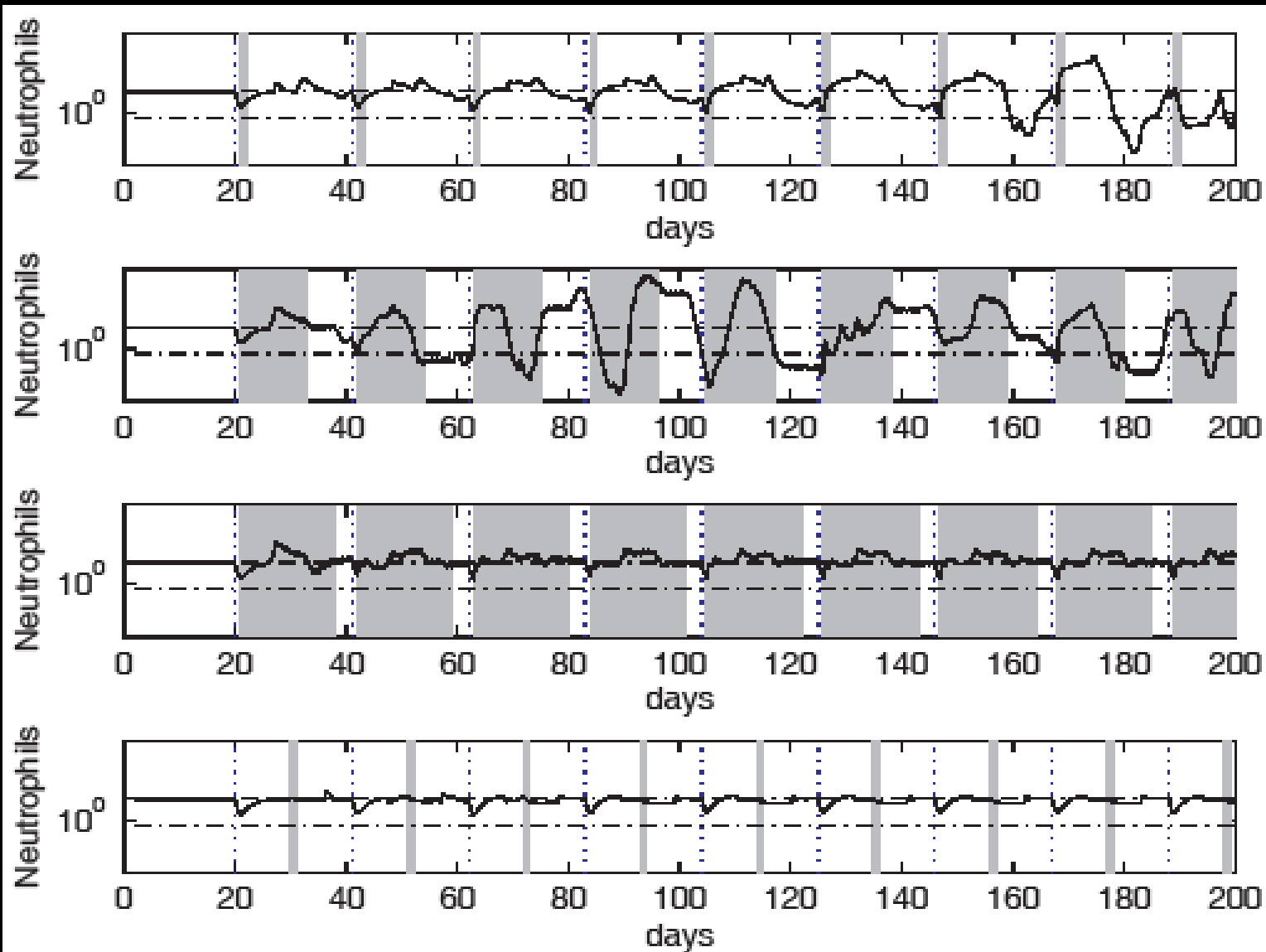
Effect of duration: Start day 1 3 weeks between chemo cycles



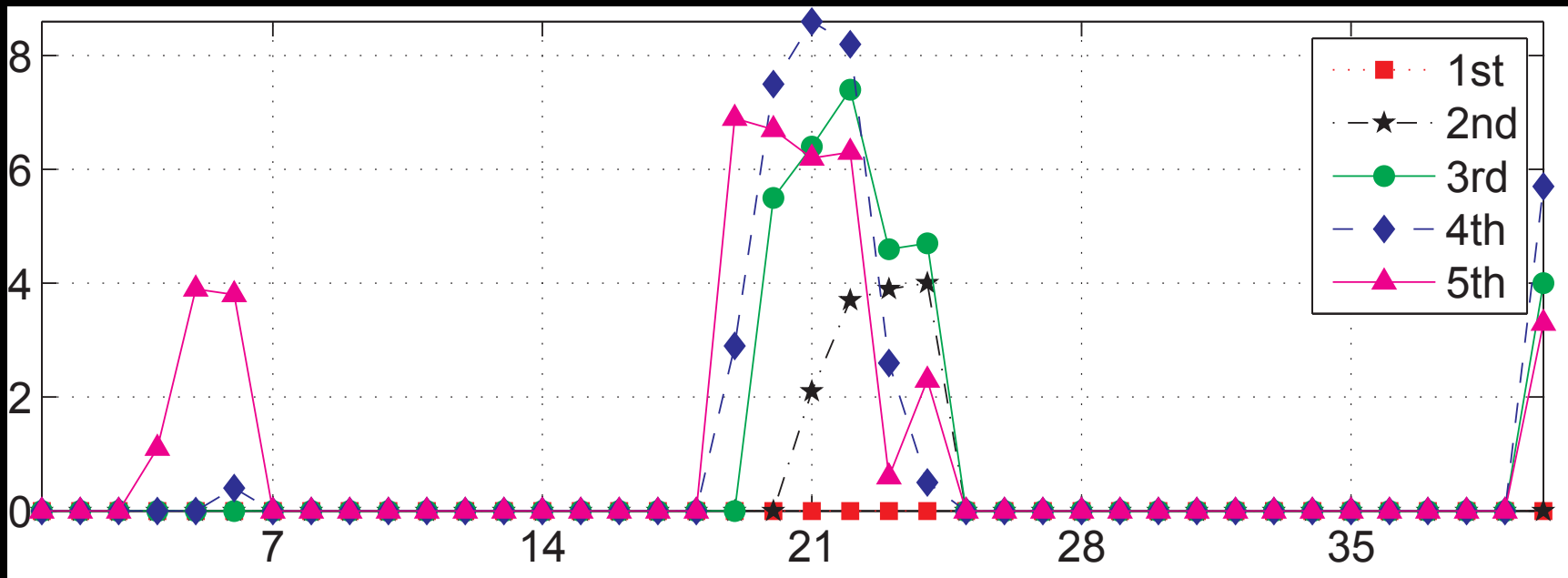
1 day Pegfilgrastim: Different timing



Duration and timing of G-CSF



Days of neutropenia vs. period of chemotherapy



G-CSF and Chemotherapy

Model is able to quantitatively reproduce serum G-CSF levels in patients

The starting day and duration of G-CSF administration have profound effects

Likewise, timing between chemotherapy can profoundly affect the outcome

Is it possible to tailor treatment to individuals?

If so much more collaboration between clinicians, basic scientists & mathematicians will be necessary.

I think that it is possible

c.f. Foley & M, J. Theor. Biol. (2009) **257**, 27-44

A very special thanks to

- NSERC
- MITACS
- The entire CAMBAM group
- And the CHEMO WORKING GROUP

