An integrated G-CSF-myelosuppression model characterizing the target mediated disposition of endogenous G-CSF in breast cancer patients following chemotherapy

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Granulocyte Colony Stimulating Factor (G-CSF)

- ✓ 20 kDa glycoprotein growth hormone
- ✓ Regulates the homeostasis of neutrophils

- ✓ Chemotherapy induced neutropenia
  - Abnormally low absolute neutrophil counts (ANC)
  - Increased risk of life-threating infections
  - Reduced and/or delayed dose => suboptimal treatment

- ✓ Recombinant G-CSF is used as supportive therapy

- ✓ Little is known of the dynamics and interplay of endogenous G-CSF and neutrophils following chemotherapy in patients with solid tumors.

- ✓ Target mediated disposition (TMD)

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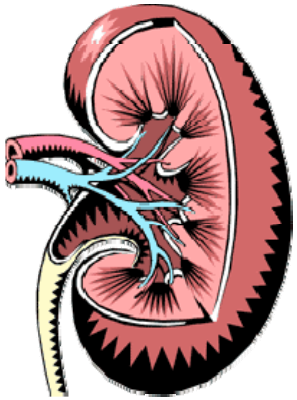
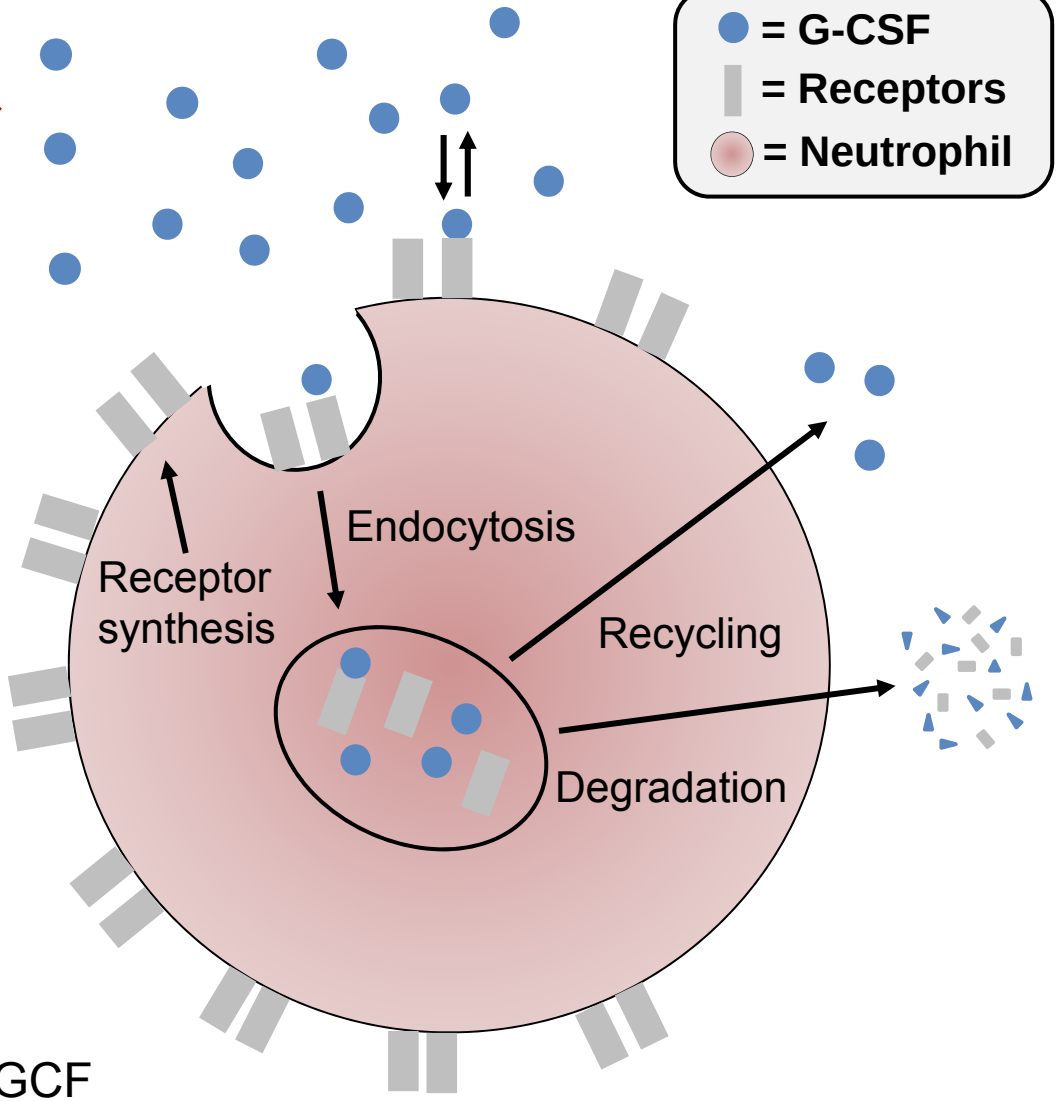
Target mediated disposition of G-CSF



Elimination



Bone marrow stromal cells, endothelial cells, fibroblasts, monocytes - macrophages

Inflammatory agents: IL-1, LPS, TNF-α, IL-4
Hematopoietic growth factors: GM-CSF, M-GCF

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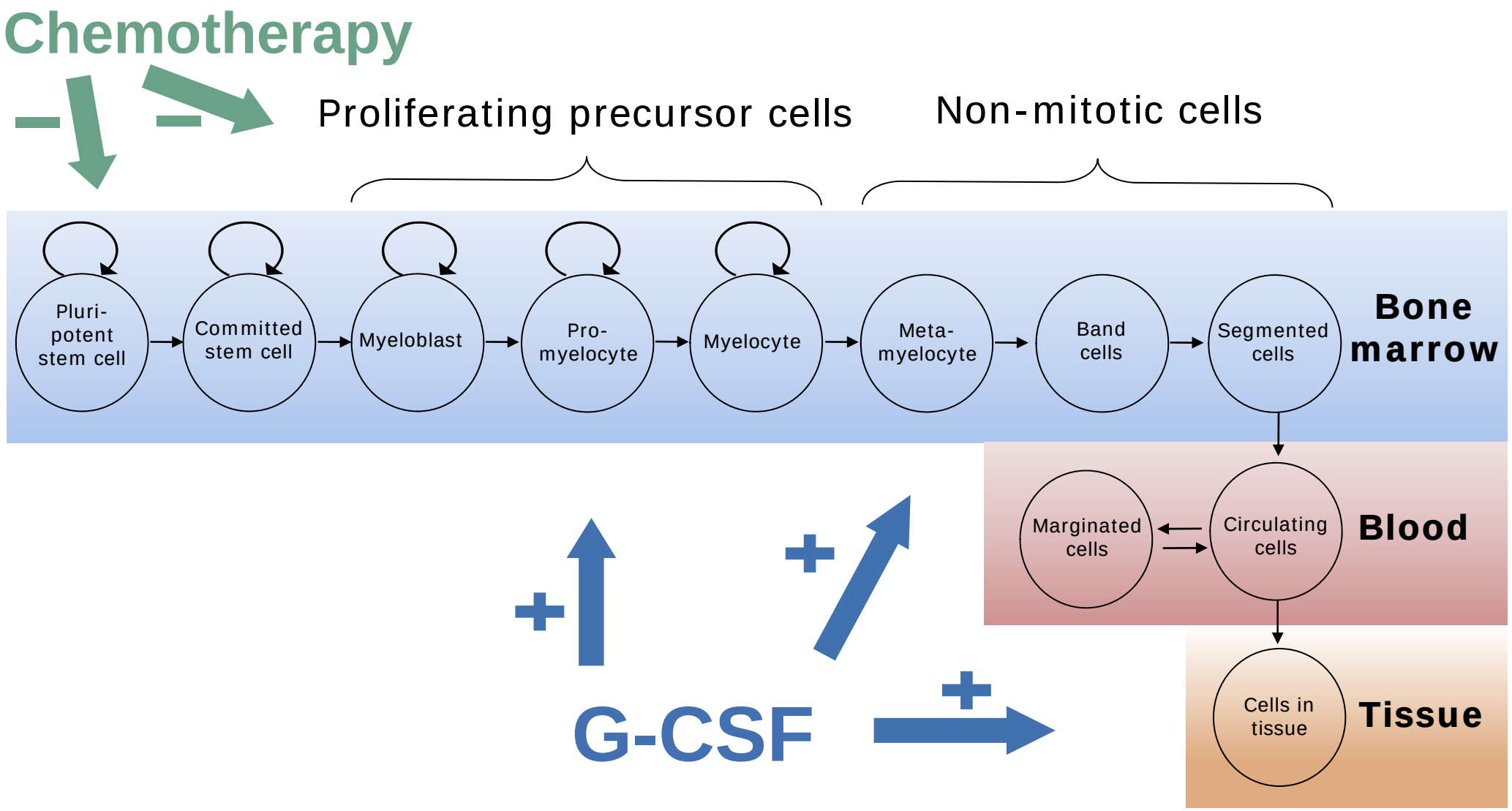
Neutrophil formation and regulation



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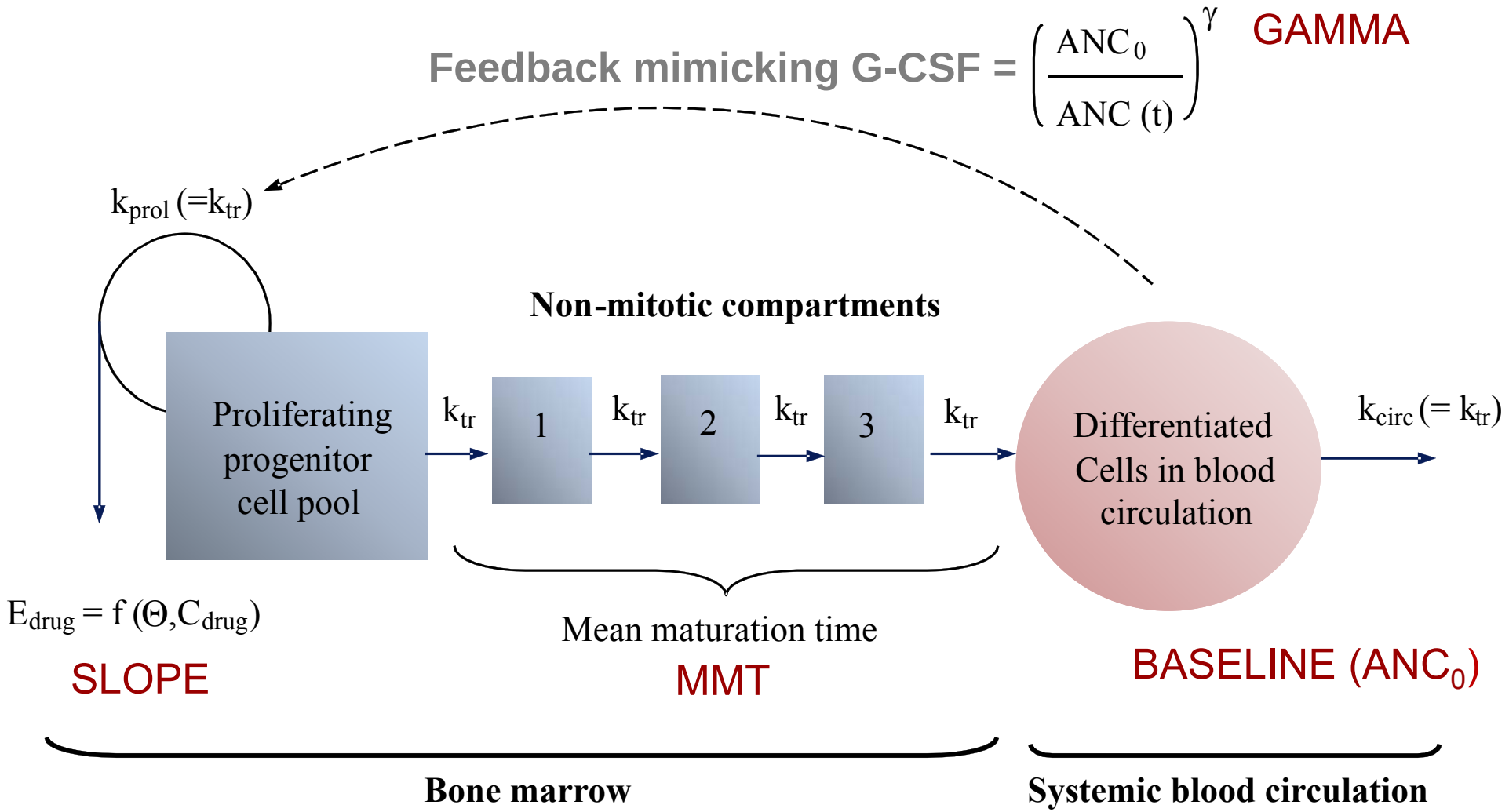
Semi-Mechanistic Myelosuppression Model



Friberg *et al.* J. Clin. Oncology 2002

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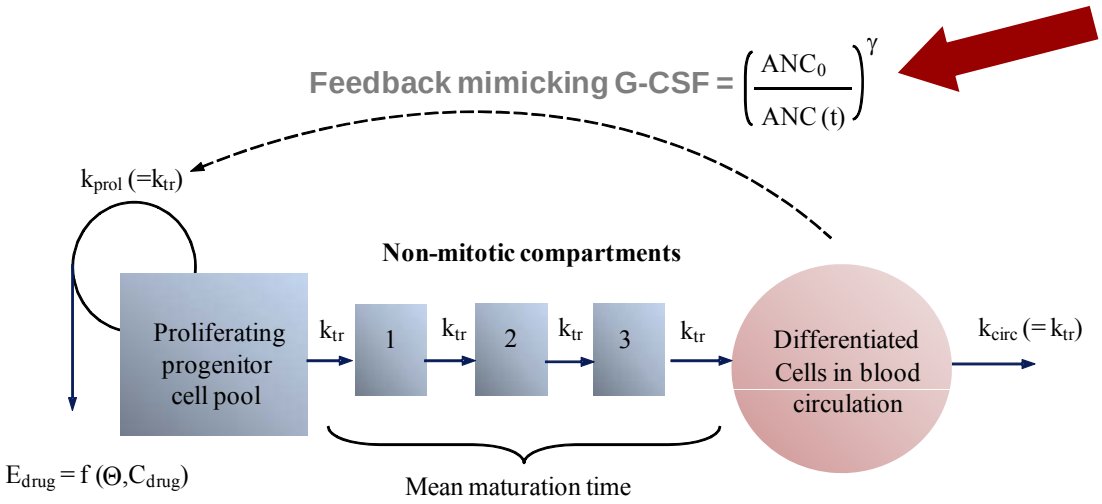
Aim

- ✓ To collect and describe the time-course and interaction between endogenous G-CSF and ANC following chemotherapy in breast cancer patients

- ✓ To increase the mechanistic properties of the semi-mechanistic myelosuppression model



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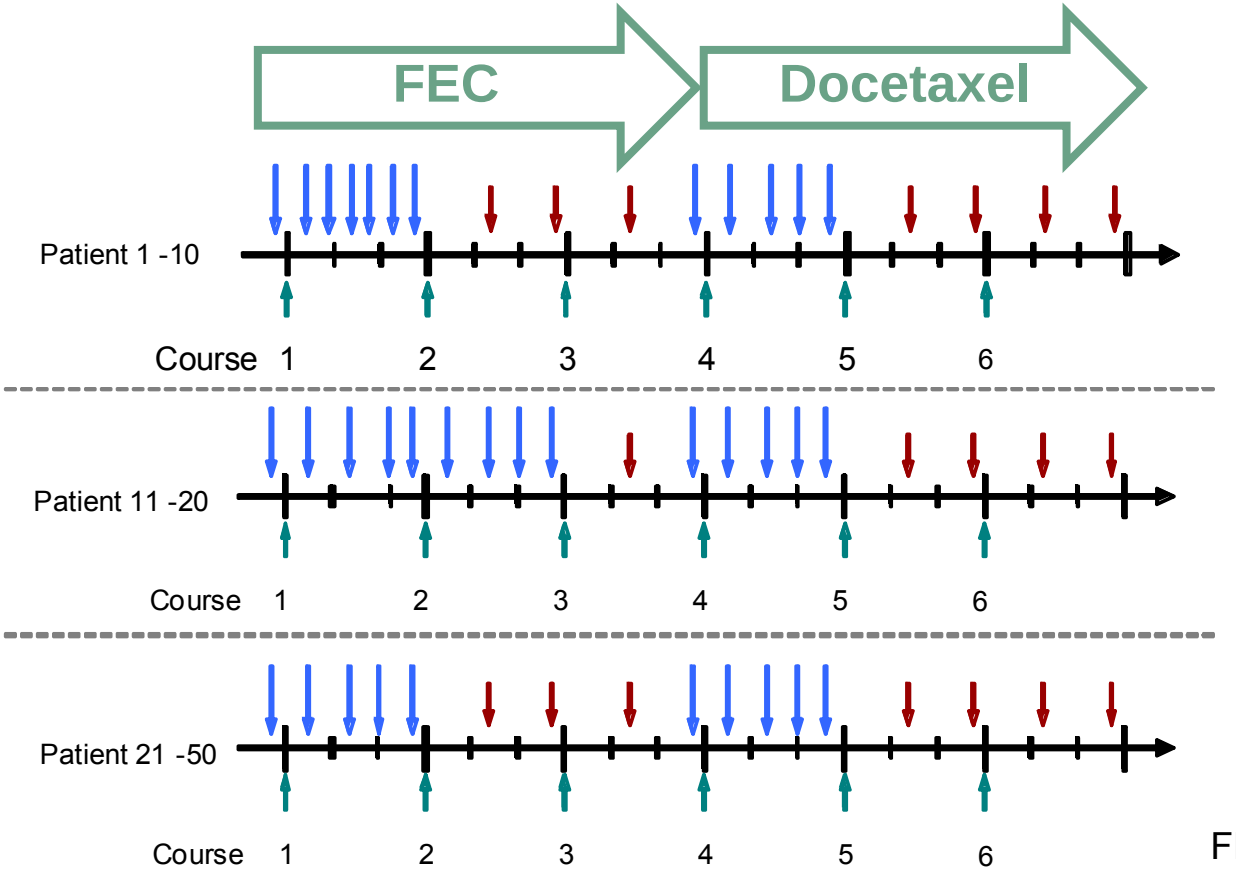
Clinical study of endogenous G-CSF and ANC

- ✓ 49 breast cancer patients receiving adjuvant treatment with chemotherapy
- ✓ 967 ANC and 514 G-CSF samples analyzed simultaneously using NONMEM 7
- ✓ No PK data available – published population PK models



ANC blood sample

G-CSF + ANC blood sample

Chemotherapy+ glucocorticoids

FEC: 5-Flourouracil+Epirubicin+Cyclophosphamide

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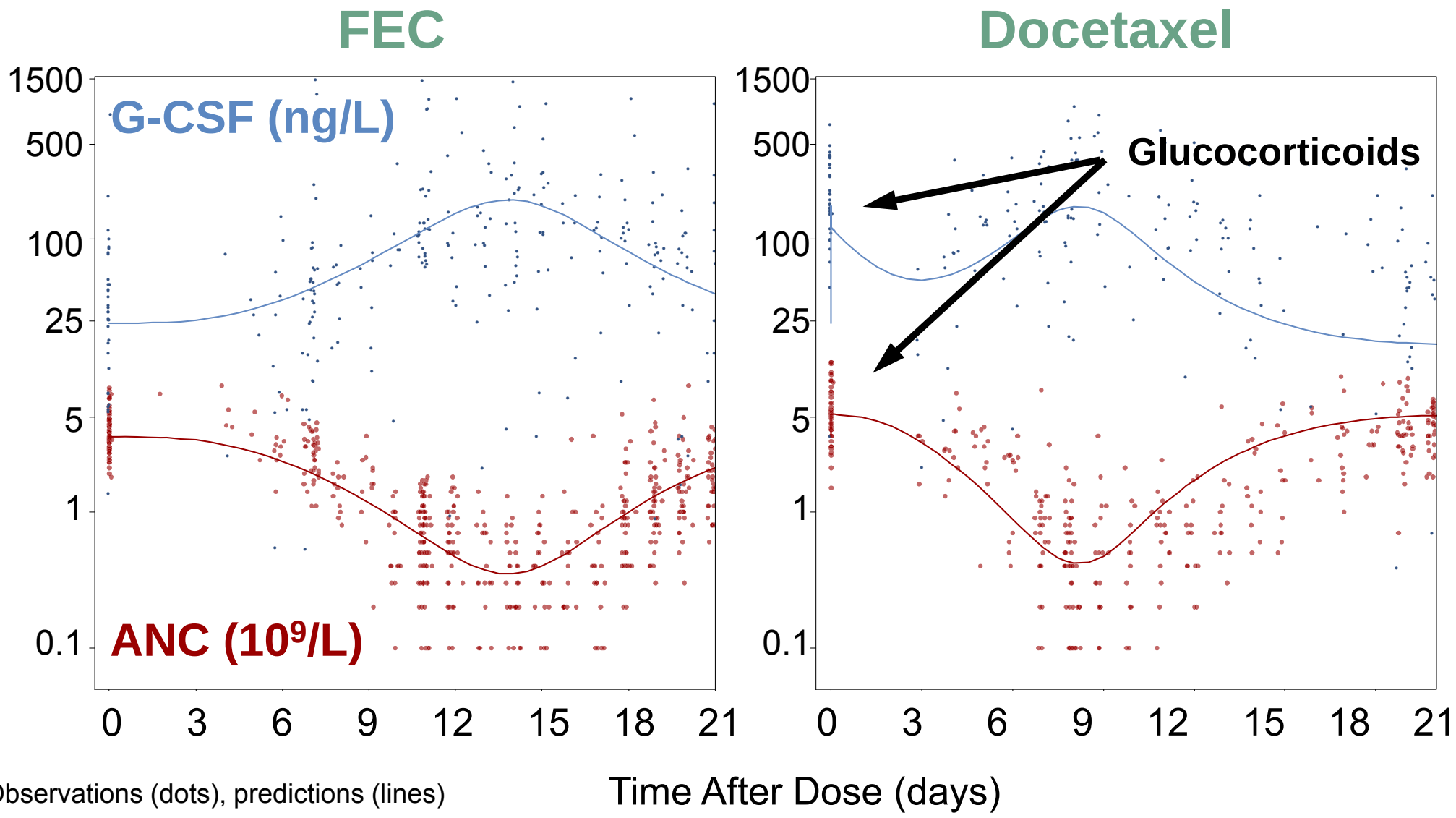
G-CSF and ANC following chemotherapy



Observations (dots), predictions (lines)

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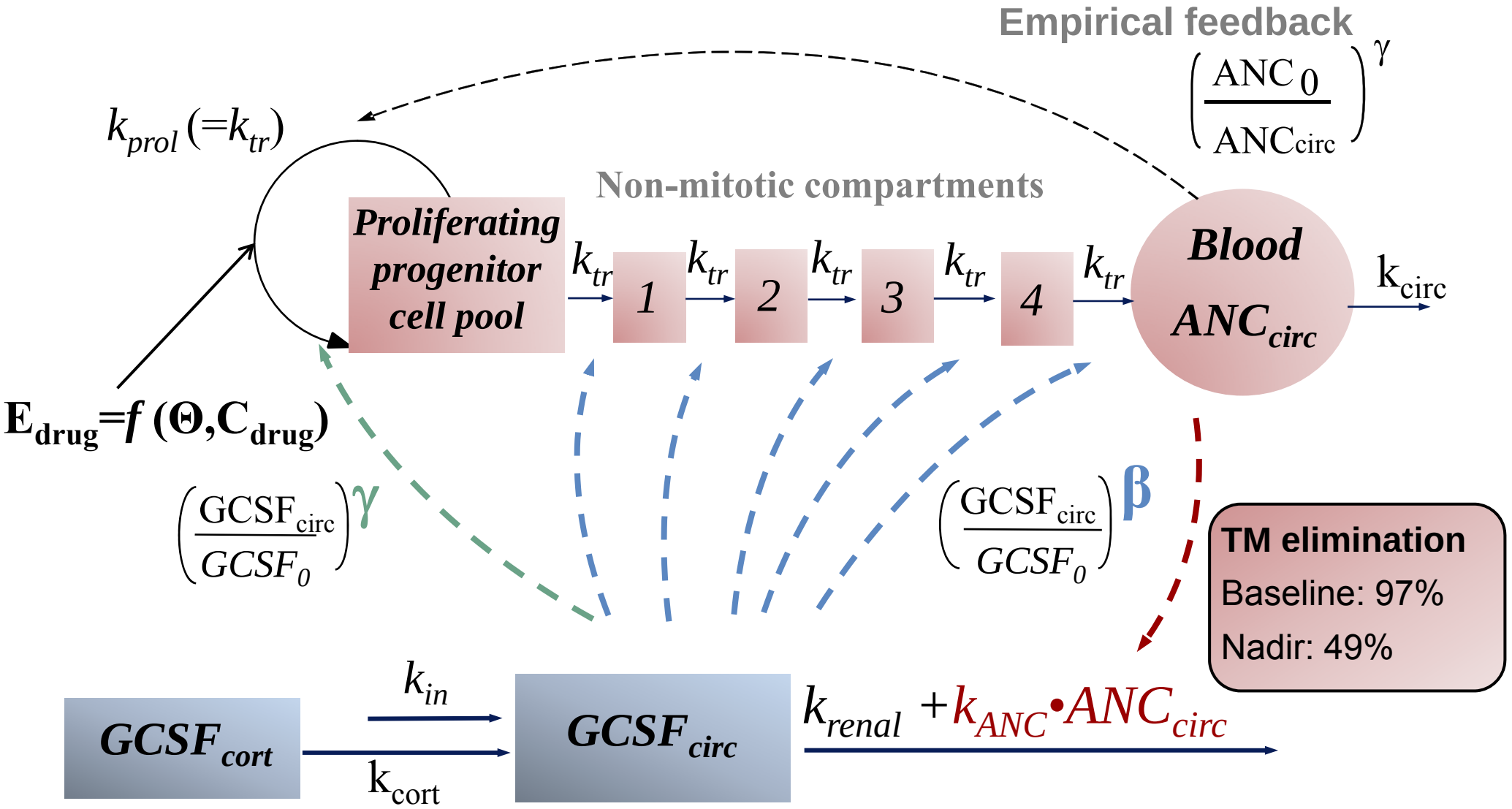
The integrated G-CSF and ANC model



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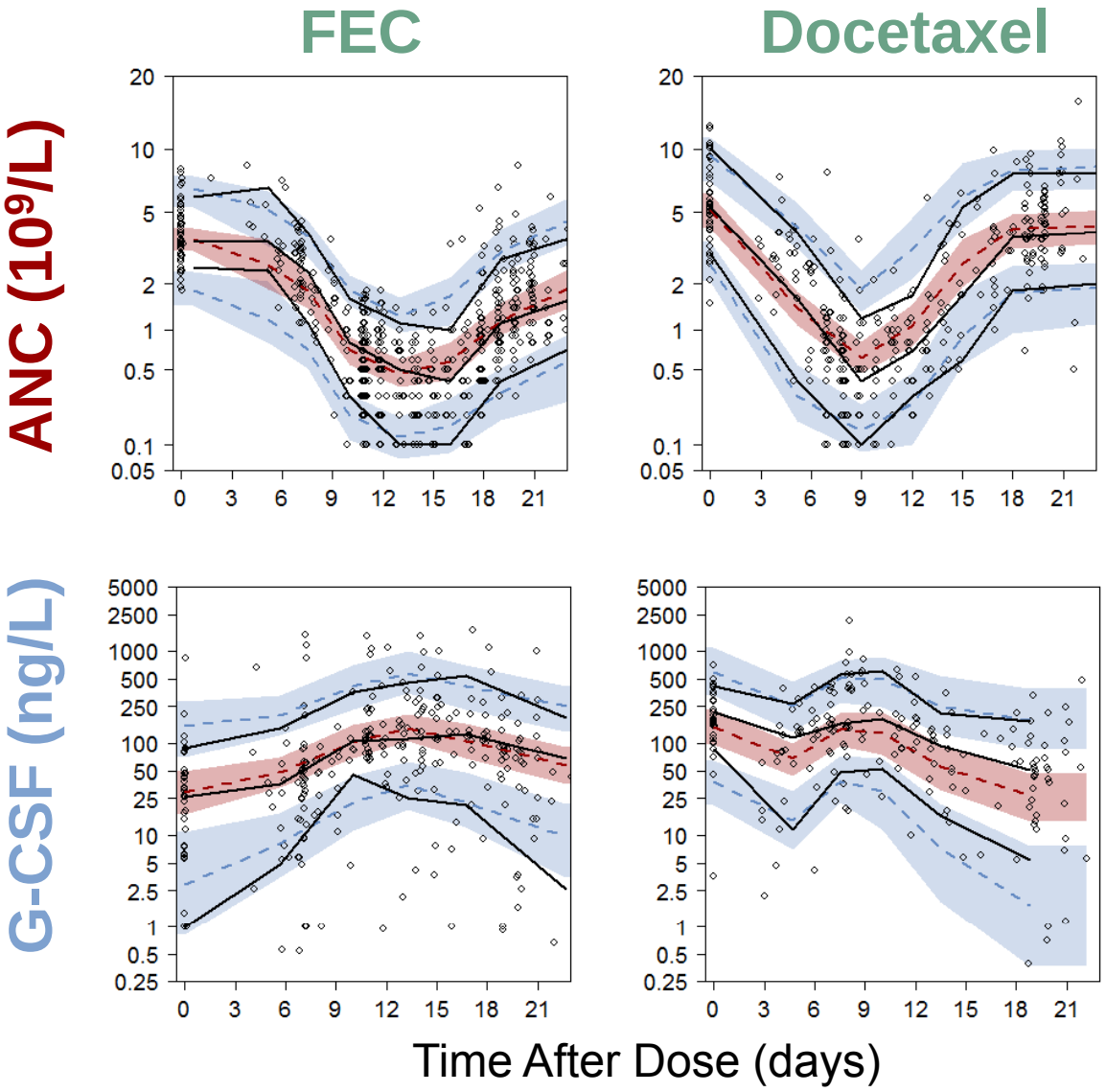
Visual predictive check (80% PI)



Observed data = dots

10th, 50th, 90th percentile of observed data (solid) and simulated data (dashed) lines

Shaded area = 95% confidence interval

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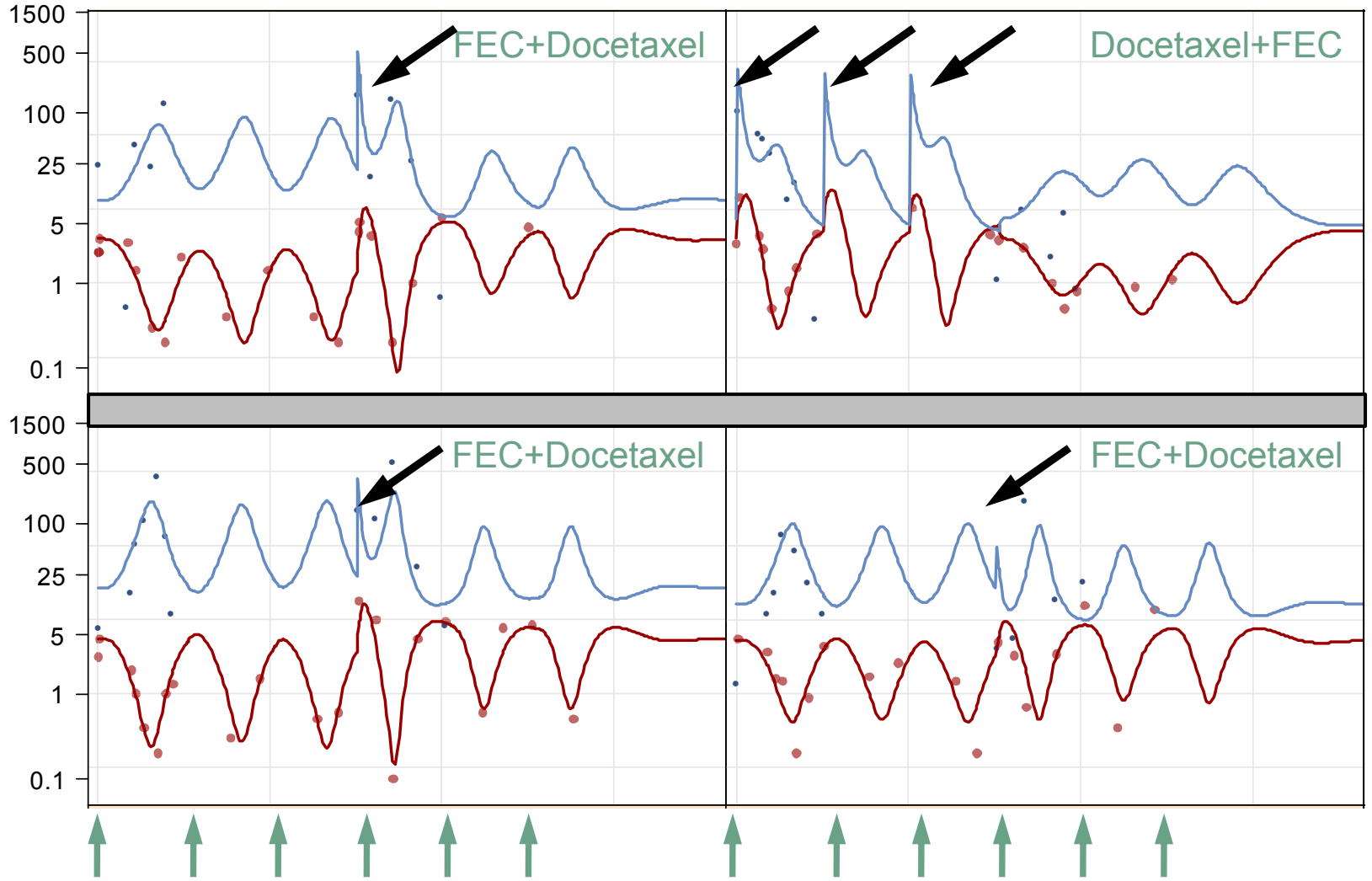
Individual time-courses of G-CSF and ANC

G-CSF (ng/L)

ANC (10^9/L)

Glucocorticoids

Chemotherapy



Observations (dots), predictions (lines)

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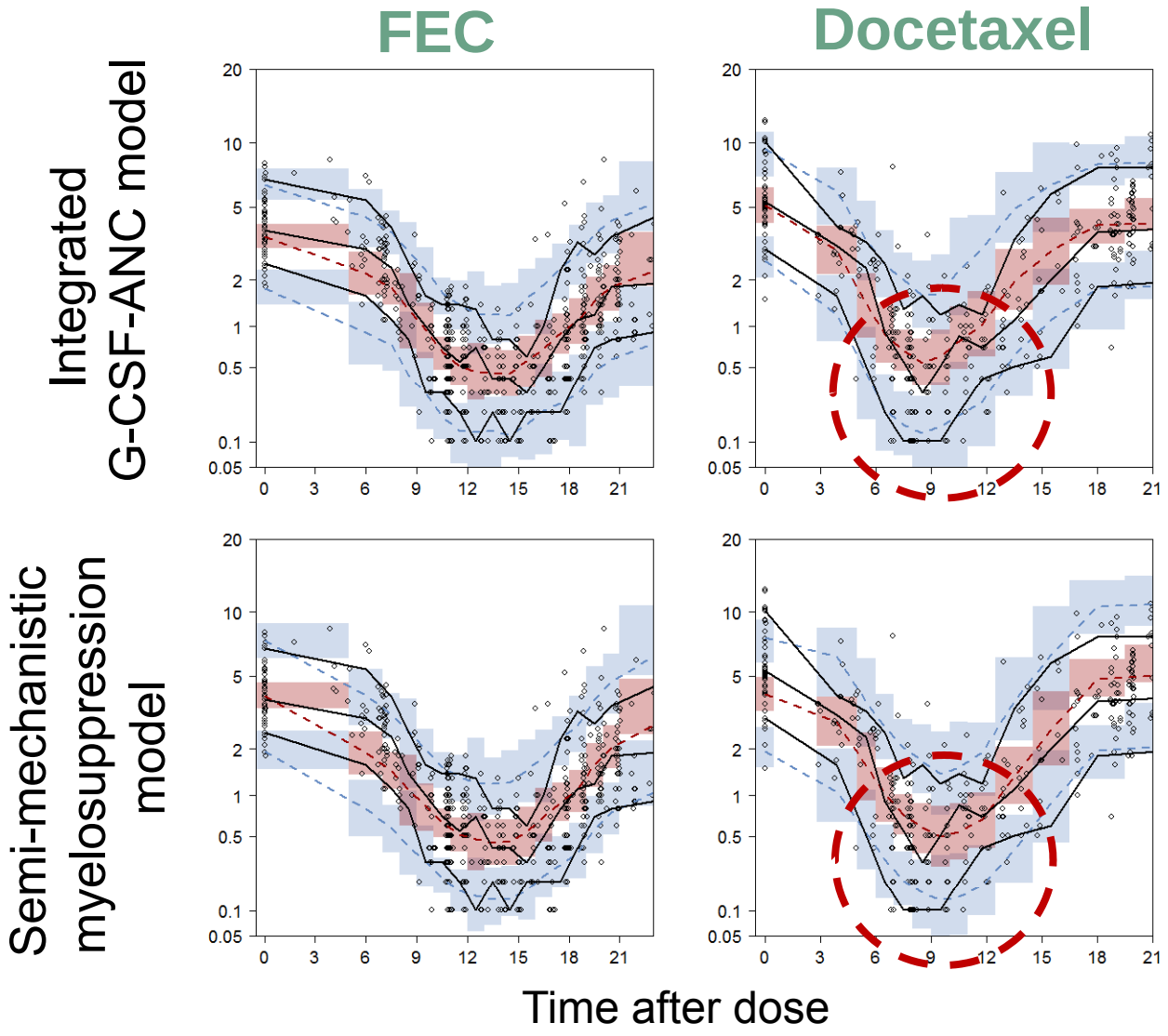
Predictions of ANC for the two models



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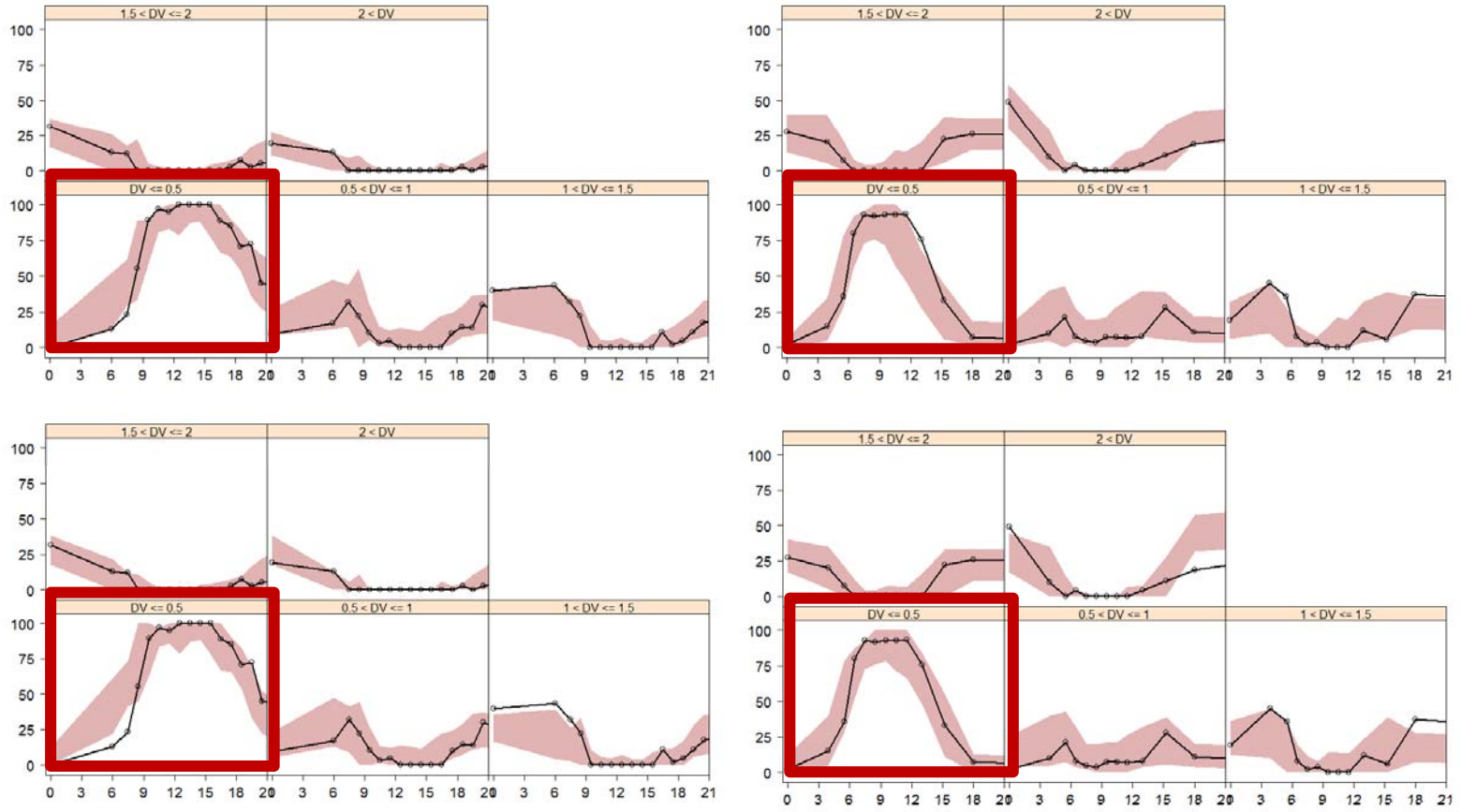
Proportion of patients with neutropenia

FEC **Docetaxel**

Integrated G-CSF-ANC model

Semi-mechanistic myelosuppression model



Time after dose

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Conclusions

- The time-courses of endogenous G-CSF and ANC were characterized and an inverse relationship was shown which confirms the self-regulatory properties of the system
- The integrated G-CSF – myelosuppression model described the target-mediated disposition of endogenous G-CSF and supports that the neutrophil-dependent elimination is the main elimination route of G-CSF
- An increased production of G-CSF by glucocorticoids was quantified and explained the subsequent increase in ANC
- A more mechanistic model for myelosuppression was developed by incorporating endogenous G-CSF measurements

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Future perspectives

Further characterization of the system

- ✓ Inflammation and infection marker
  - ✓ Interleukin-6
  - ✓ C-reactive protein
- ✓ Predictors for (febrile) neutropenia

Schedule optimization

- ✓ Investigate predictive performance for other schedules/drugs
- ✓ Chemotherapy
- ✓ Recombinant G-CSF

Acknowledgement

To all women who participated in the study

Swedish Cancer Society

Thank you for listening!