Extending the Systems Model of Platelet Homeostasis to Understand Platelet Dynamics in Immune Thrombocytopenia Purpura (ITP)

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Outline

Immune Thrombocytopenia Purpura (ITP)

Disease Characteristics

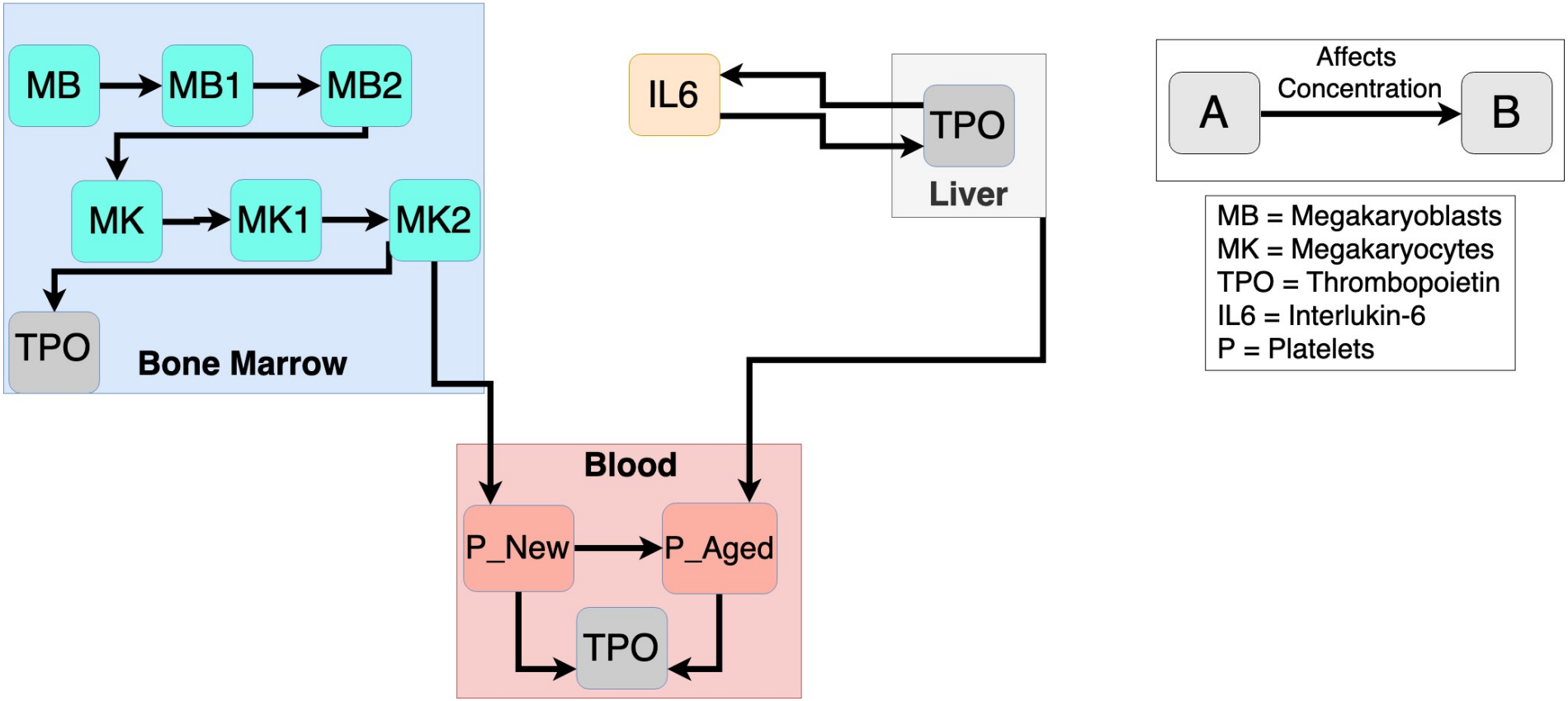
- Autoimmune disease that leads to lower than normal platelet count

General Facts

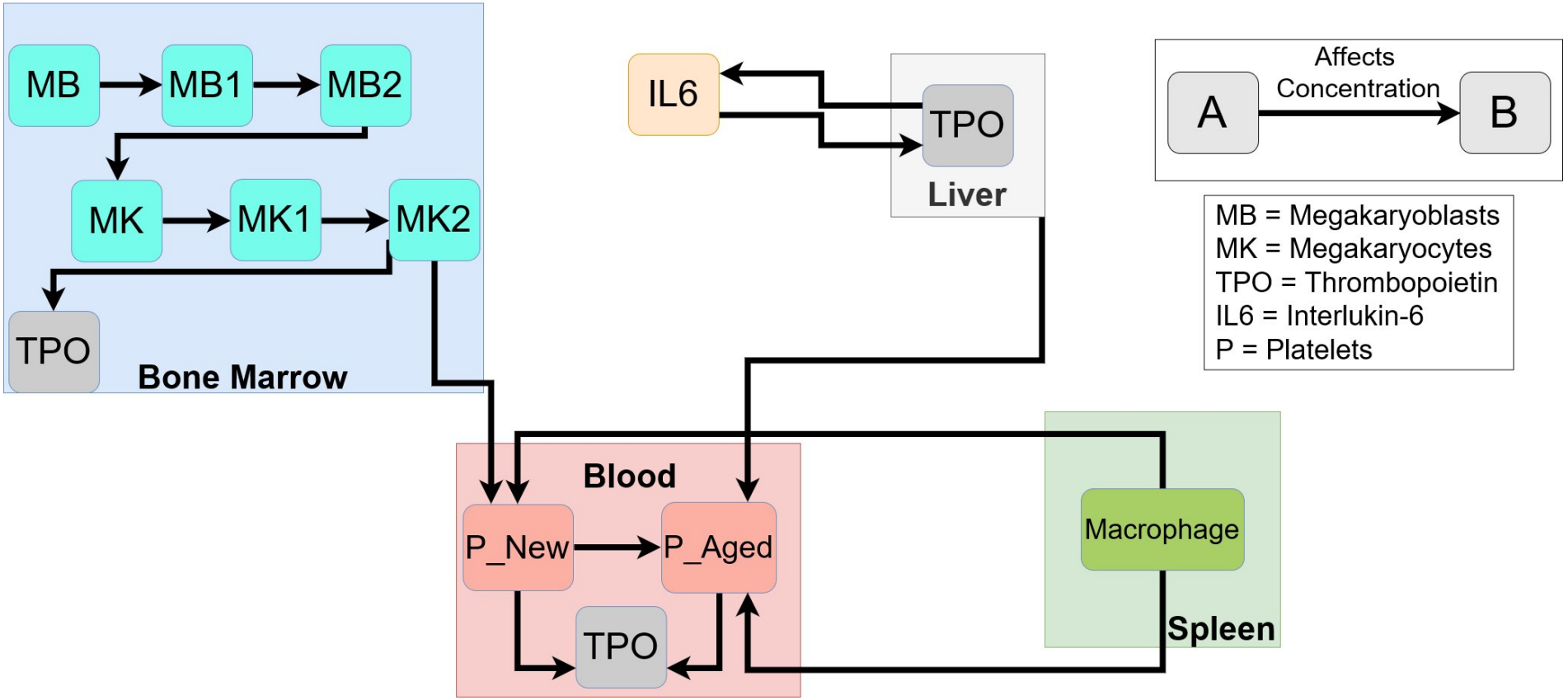
- Approx. 2-12/100,000 adults and children affected, respectively, per year
- Mortality rate of 1-3% per year
- Symptoms: purple spots, easy bruising and bleeding
- Risks: internal bleeding in body and brain

Čulić, S., et. al (2013). Immune thrombocytopenia: Serum cytokine levels in children and adults. Medical Science Monitor, 19, 797-801. doi:10.12659/msm.884017
Cines, D. B., Blanchette, V. S. (2002). Immune Thrombocytopenic Purpura. Medical Progress, 326(13).

Platelet Production System



Platelet Production System



Thrombopoietin (TPO)

Importance in Platelet Homeostasis System

- The primary regulator of platelet production
  - Binds to Megakaryocyte (MK) receptors
  - Stimulates increase numbers and size
- Main Source: liver
- Also found in bone marrow and blood
  - Three species of TPO found in model

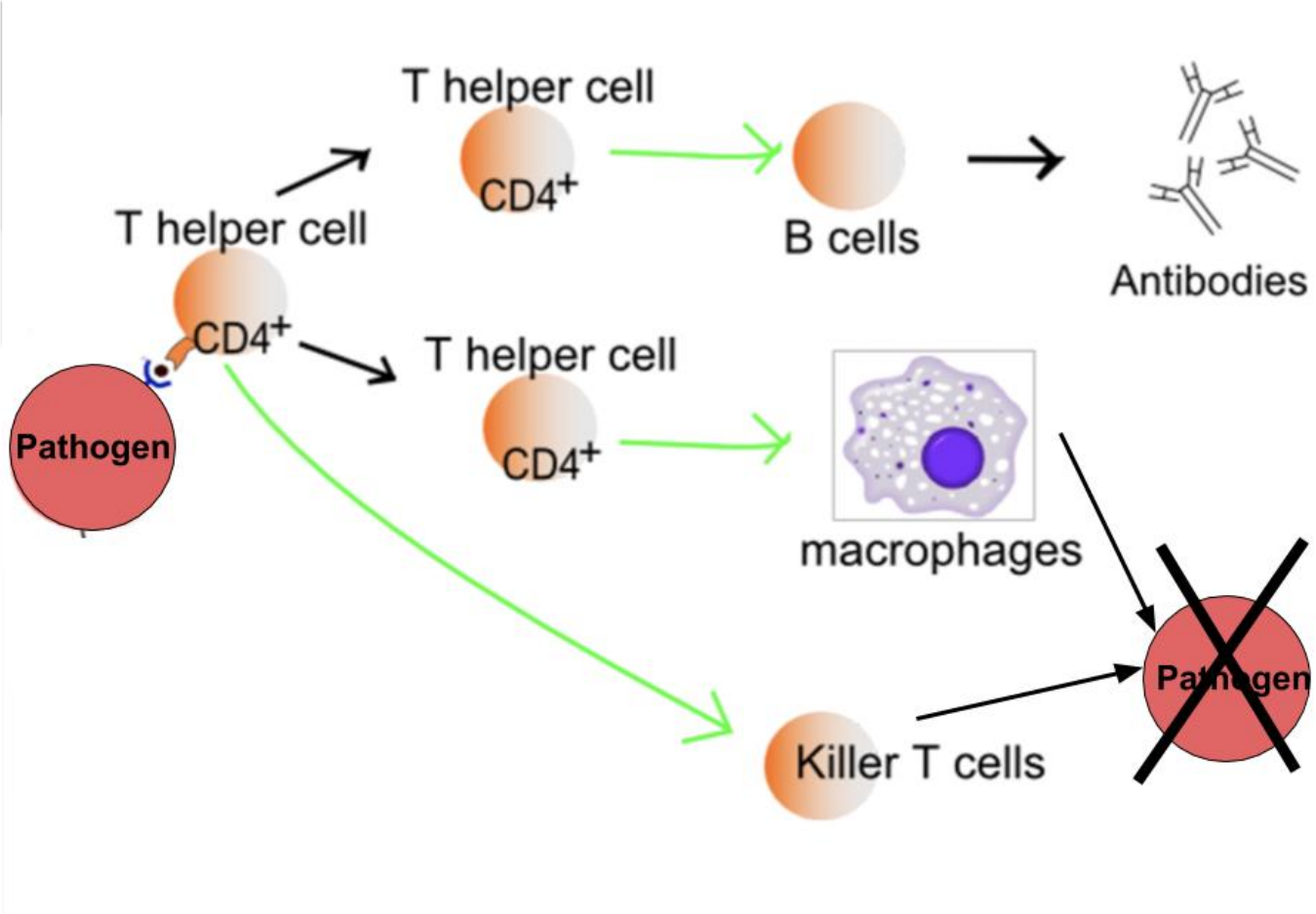
In a Healthy Individual - Inverse Relationship

- **High** platelet counts $\rightarrow$ **Low** TPO levels
- **Low** platelet counts $\rightarrow$ **High** TPO levels

In an ITP Patient

- **Low** platelet counts $\rightarrow$ **Unchanged** TPO levels (remain in healthy range)
- Feedback mechanism does not function properly

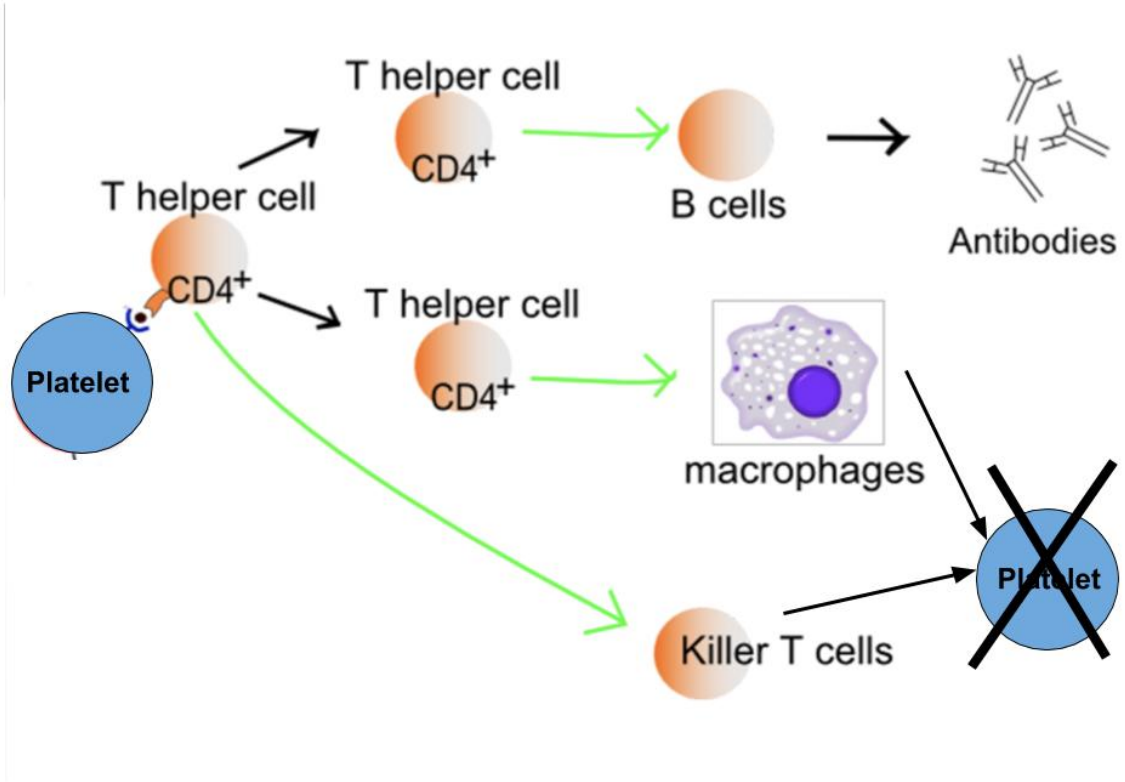
Immune Response



Adapted from: https://courses.lumenlearning.com/boundless-ap/chapter/adaptive-immunity/

Immune Response Malfunction in ITP

Platelets are perceived as pathogens in ITP



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Project Goals

Big Questions

- What is the biology behind platelet clearance via the immune system?
- How is this affected within patients with ITP?
- How can we extend this knowledge to the original model?

Goals

- Simulate the malfunction in platelet homeostasis in ITP patients
  - Accelerated platelet destruction
  - Lower total platelet count
  - Inhibited platelet production
  - No changes to TPO levels

New Model: Effect of Macrophages

Subset of Reactions

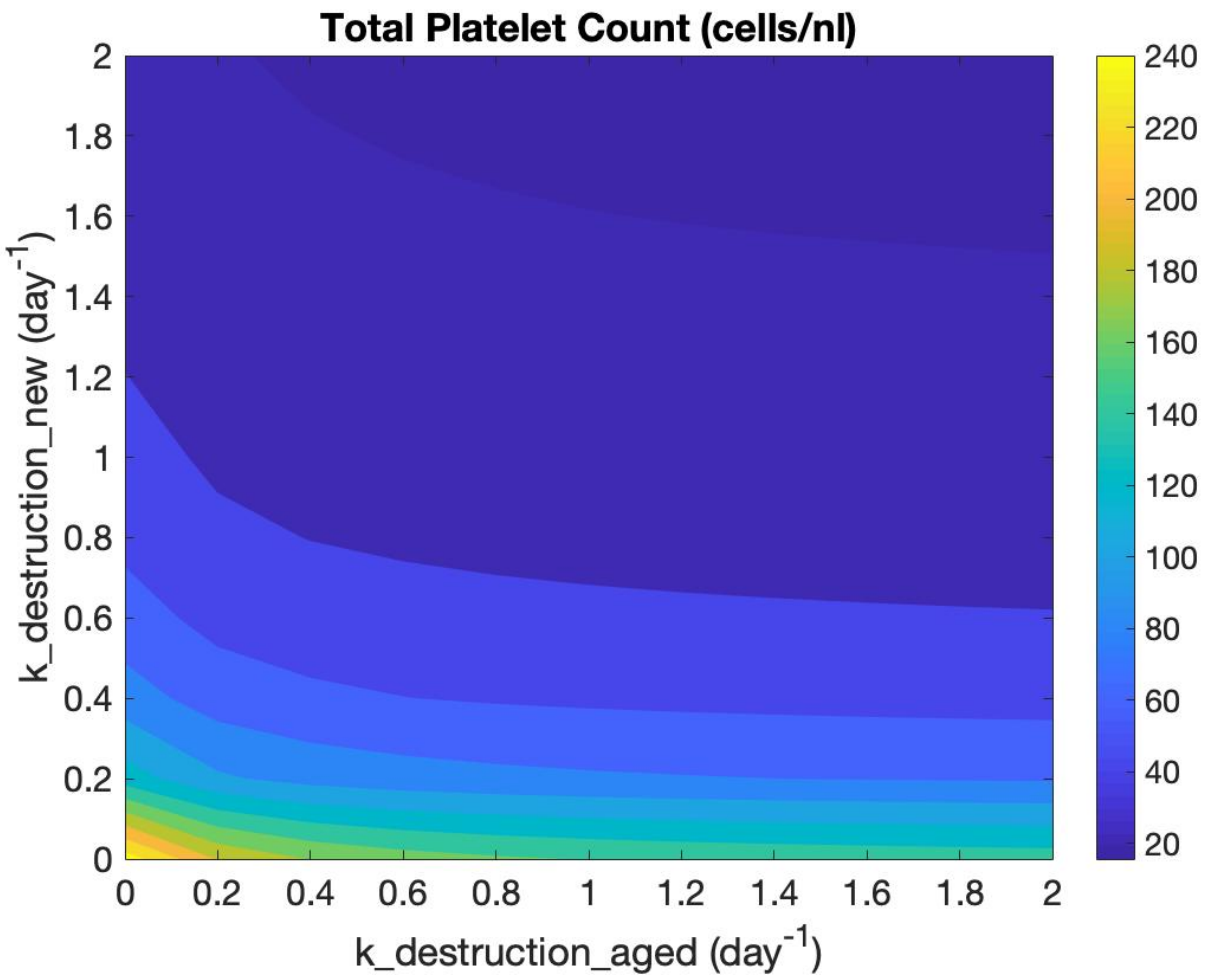
MK2 $\rightarrow$ P_new	(MK Differentiation into platelets)
P_new $\rightarrow$ P_aged	
P_aged $\rightarrow \emptyset$	(Removal by Liver AMR)
P_aged $\rightarrow \emptyset$	(Immune Clearance)
P_aged $\rightarrow \emptyset$	(Phagocytosis)
P_new $\rightarrow \emptyset$	(Phagocytosis)

Modified ODEs

$$\frac{\mathrm{d}P\_aged}{\mathrm{d}t} = ((k_{P\_aging} \times P\_new) - (k_{destruction\_aged} \times P\_aged) - \left(k_{P\_AMR} \times \left(\frac{P\_aged^{p1}}{P1^{p1} + P\_aged^{p1}}\right)\right) - (k_{P\_immune} \times P\_aged))$$

$$\frac{\mathrm{d}P\_new}{\mathrm{d}t} = (-(k_{P\_aging} \times P\_new) - (k_{destruction\_new} \times P\_new) + \left(P\_MK \times \left(k_{MKd} \times MK2 + Emax \times k_{MKd} \times MK2 \times \frac{(TPO\_BM \times k_{rate\_diff\_MK})^{m1}}{(k_{diff\_MK})^{m1} + (TPO\_BM \times k_{rate\_diff\_MK})^{m1}}\right)\right))$$

Results: New and Aged Platelets Destruction Rates

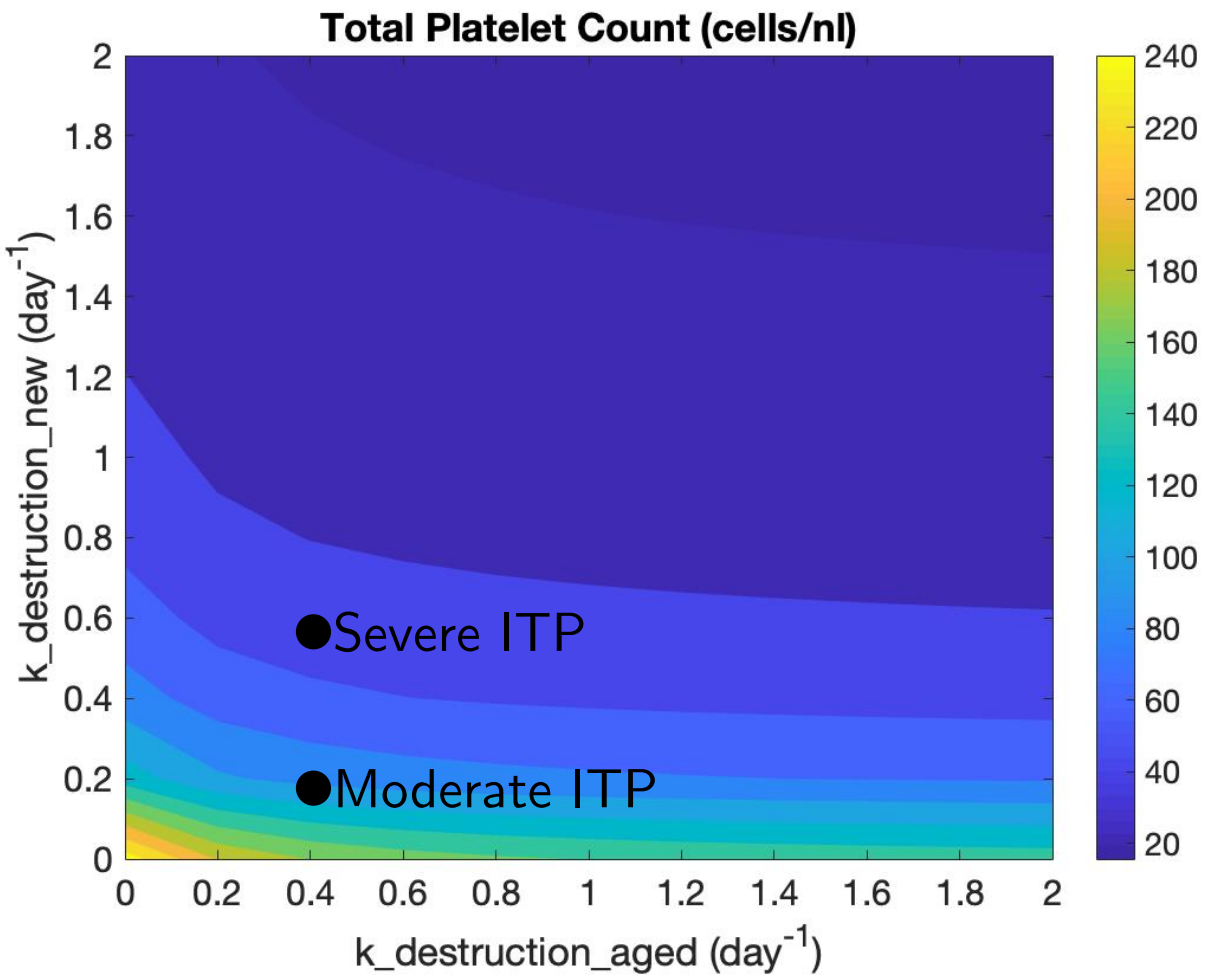


- Normal Total Platelet Count: **150-400 cells/nl**
- Severity Indicator: **50 cells/nl**

Conclusion

- Clearance of **new platelets** has a **larger impact** on total platelet levels than clearance of aged platelets

Results: New and Aged Platelets Destruction Rates



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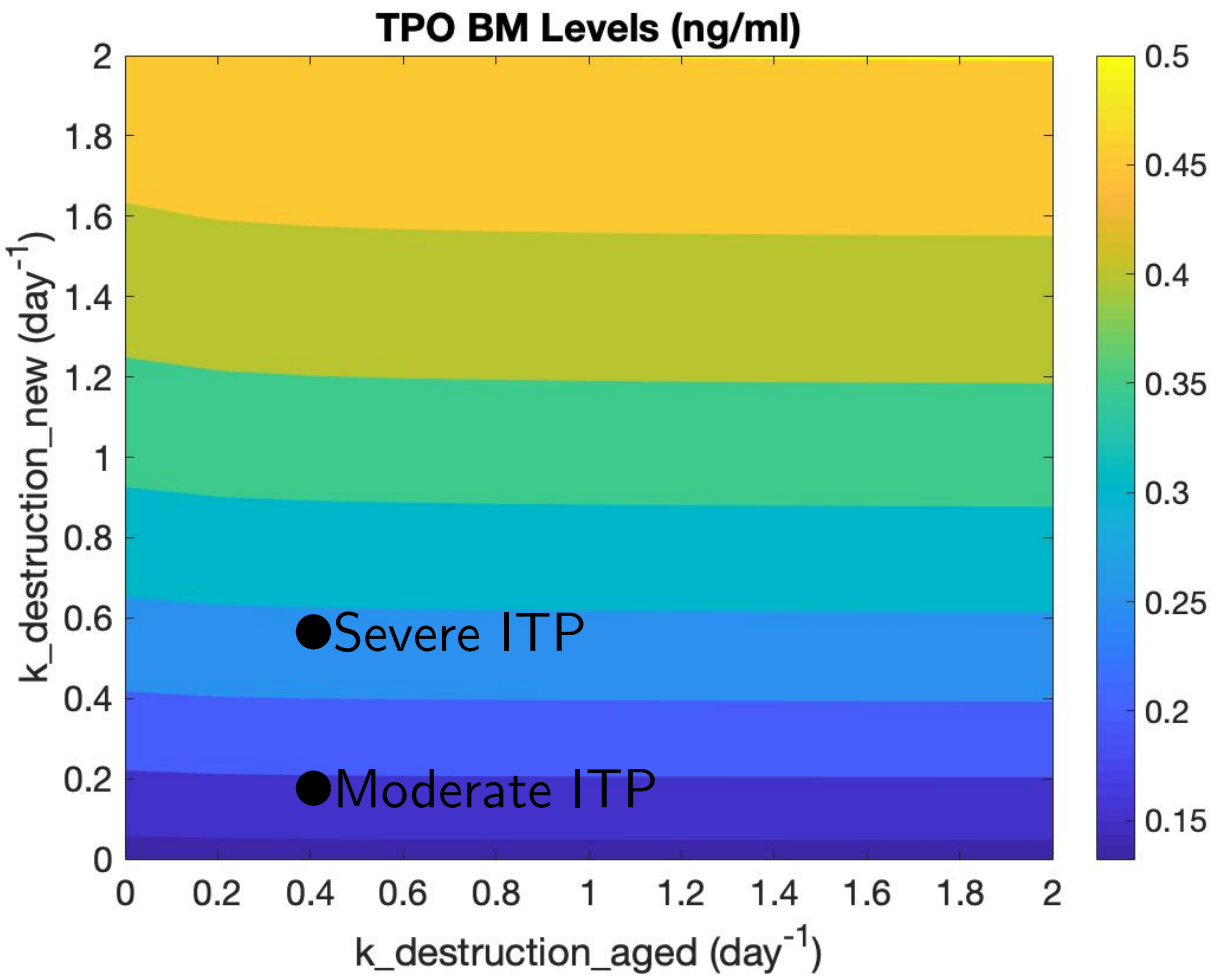


- Healthy Bone Marrow TPO: **0.1315 ng/ml**

Conclusions

- Clearance of **new platelets** has a **larger impact** on TPO levels in the bone marrow than clearance of aged platelets

Subset of Model Reactions

TPO Change Model Reactions

TPO_Liver $\rightarrow$ TPO_Blood (Reaction 7)

TPO_Blood $\rightarrow$ TPO_BM (Reaction 8)

TPO_Blood $\rightarrow \emptyset$ (Consumption by platelets) (Reaction 15)

TPO_BM $\rightarrow \emptyset$ (Consumption by MK) (Reaction 16)

ODEs with TPO Change

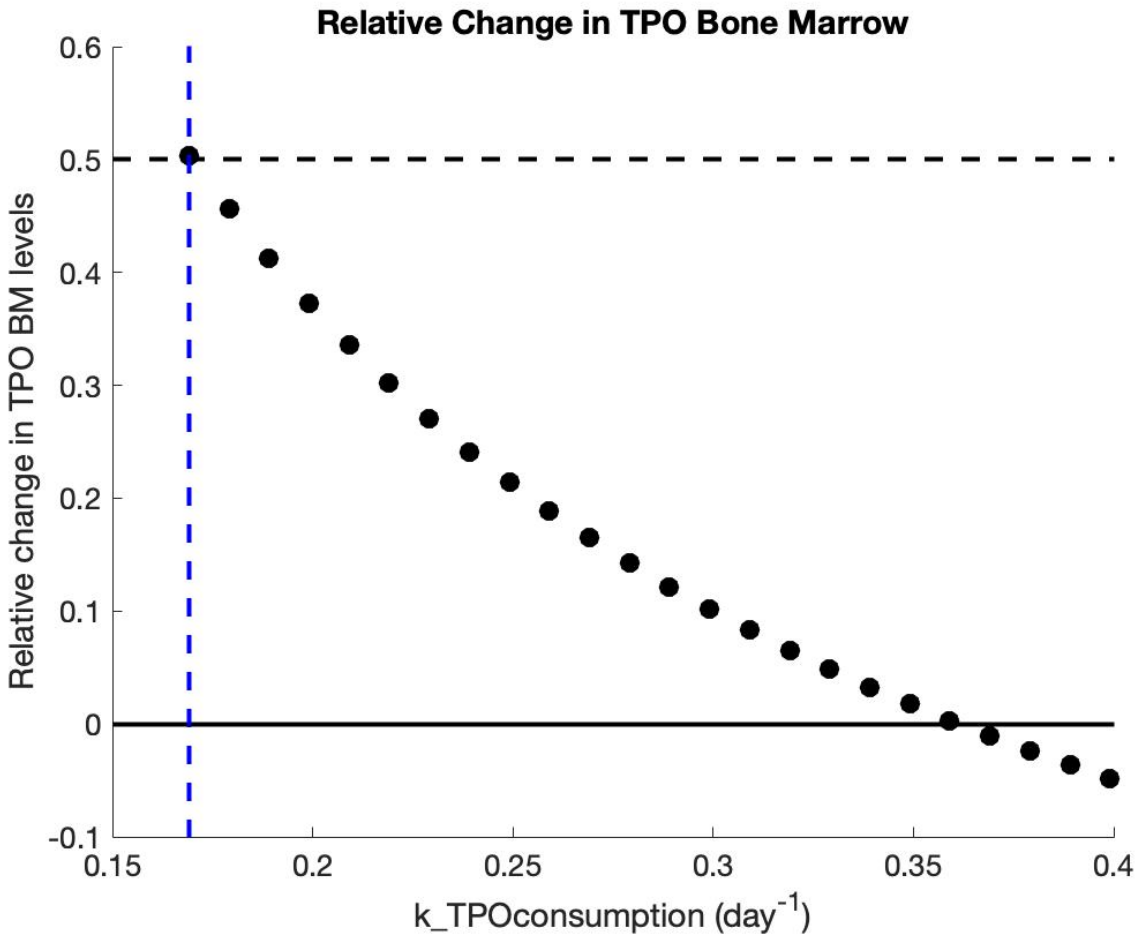
$$\frac{\mathrm{d}\,TPO\_Blood}{\mathrm{d}t} = \frac{1}{Blood}(Reaction7 - Reaction8 - Reaction15)$$

$$\frac{\mathrm{d}\,TPO\_BM}{\mathrm{d}t} = \frac{1}{BoneMarrow}(Reaction8 - Reaction16)$$

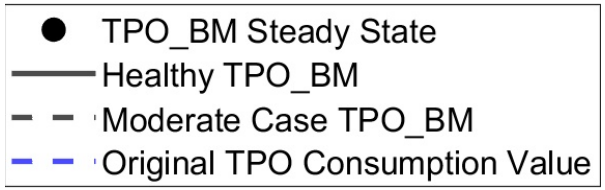
Reaction 15 Rate

$$K_{15} = \mathbf{k\_TPOconsumption} \times \left(\frac{(Rate\_k\_TPOconsumption \times TPO\_Blood)^{h2}}{(k\_plt\_TPO)^{h2} + (Rate\_k\_TPOconsumption \times TPO\_blood)^{h2}}\right) \times (P\_new + (w\_TPOconsumption \times P\_aged)) + d\_TPO \times TPO\_Blood$$

Results: Moderate Case



- k_destruction_aged: **0.4 day^{-1}**
- k_destruction_new: **0.2 day^{-1}**
- Total Platelets: **93 cells/nl**



Conclusion

- Increasing consumption rate can help decrease TPO levels to healthy range, but does not seem biologically feasible

Subset of Model Reactions

TPO Change Model Reactions

TPO_Blood → TPO_BM (Reaction 8)

TPO_Blood → ø (Consumption by platelets) (Reaction 15)

ODEs with TPO Change

$$\frac{\mathrm{d}\,TPO\_Blood}{\mathrm{d}t} = \frac{1}{Blood}(Reaction7 - Reaction8 - Reaction15)$$

$$\frac{\mathrm{d}\,TPO\_BM}{\mathrm{d}t} = \frac{1}{BoneMarrow}(Reaction8 - Reaction16)$$

Reaction Rates

$$K_{15} = \mathbf{k\_TPOconsumption} \times \left(\frac{(Rate\_k\_TPOconsumption \times TPO\_Blood)^{h2}}{(k\_plt\_TPO)^{h2} + (Rate\_k\_TPOconsumption \times TPO\_blood)^{h2}}\right) \times (P\_new + (w\_TPOconsumption \times P\_aged)) + d\_TPO \times TPO\_Blood$$

$$K_8 = \mathbf{kTPO1} \times TPO\_Blood$$

Results: Moderate ITP

- k_destruction_aged = 0.4 day^{-1}
- k_destruction_new = 0.2 day^{-1}

Adjusted Parameters

- **Original Values (day^{-1})**
  - k_TPOconsumption = 0.1691
  - kTPO1 = 0.3123
- **Adjusted Values (day^{-1})**
  - k_TPOconsumption = 0.25
  - kTPO1 = 0.25

	TPO Blood		**TPO BM**	
	Value (ng/ml)	Percent Change	Value (ng/ml)	Percent Change
Healthy	0.1698	0%	0.1315	0%
Moderate ITP	0.227	33%	0.1977	50%
Adjusted Moderate ITP	0.2031	19.6%	0.1253	-4.7%

Conclusion

- To achieve similar results in TPO BM, varying only k_TPOconsumption, would otherwise require 113% increase in the parameter
- Varying multiple parameters with a more biologically feasible range results in desired TPO levels

Results: Severe ITP

- k_destruction_aged = 0.4 day^{-1}
- k_destruction_new = 0.6 day^{-1}

Adjusted Parameters

- **Original Values (day^{-1})**
  - k_TPOconsumption = 0.1691
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	TPO Blood		**TPO BM**	
	Value (ng/ml)	Percent Change	Value (ng/ml)	Percent Change
Healthy	0.1698	0%	0.1315	0%
Severe ITP	0.2963	74%	0.2950	124%
Adjusted Severe ITP	0.2677	57.65%	0.1811	37.71%

Conclusion

- To achieve similar results in TPO BM, varying only k_TPOconsumption, would otherwise require 136% increase in the parameter
- Varying multiple parameters with a more biologically feasible range results in desired TPO levels

Conclusions

- Developed PHIC model by incorporating macrophage dynamics into the current platelet homeostasis model
- Decreased total platelet count leads to increased levels of TPO, which is undesirable in modeling ITP
- Adjusting TPO consumption rates might compensate for the increased levels of TPO correlated with platelet destruction
  - Increasing one parameter seems biologically infeasible
  - Adjusting a combination of parameters achieves desired healthy TPO levels in a biologically feasible way

Acknowledgements

We would like to thank the National Science Foundation, award DMS-1757685, Pfizer Inc., and the Center for Industrial Mathematics and Statistics at WPI for their support.

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Thank you for your time!

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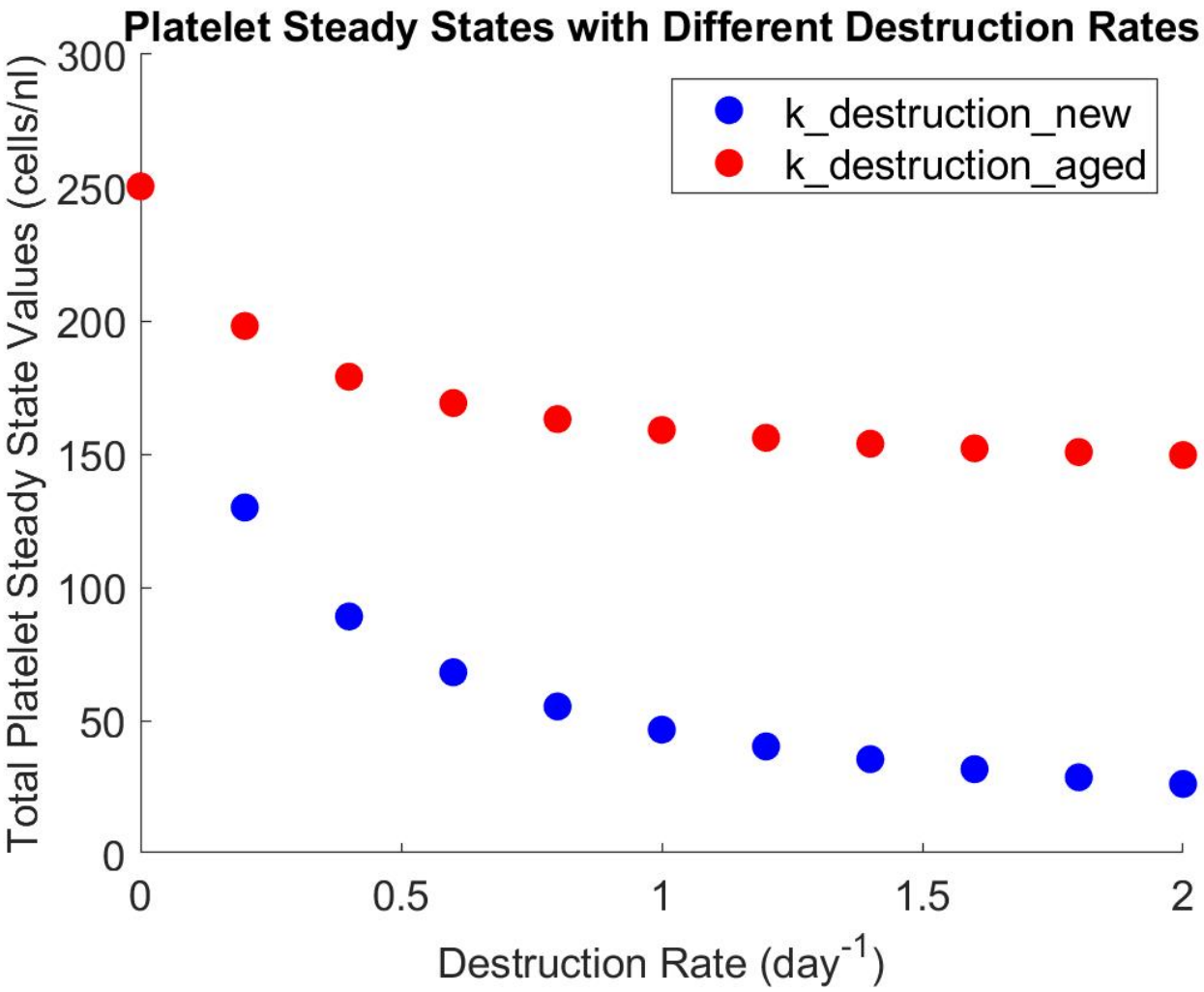
Zhou, B., et. al (2005). Multi-dysfunctional pathophysiology in ITP. *Critical Reviews in Oncology/Hematology*, 54(2), 107-116. doi:10.1016/j.critrevonc.2004.12.004

Results: Individual Destruction Rates



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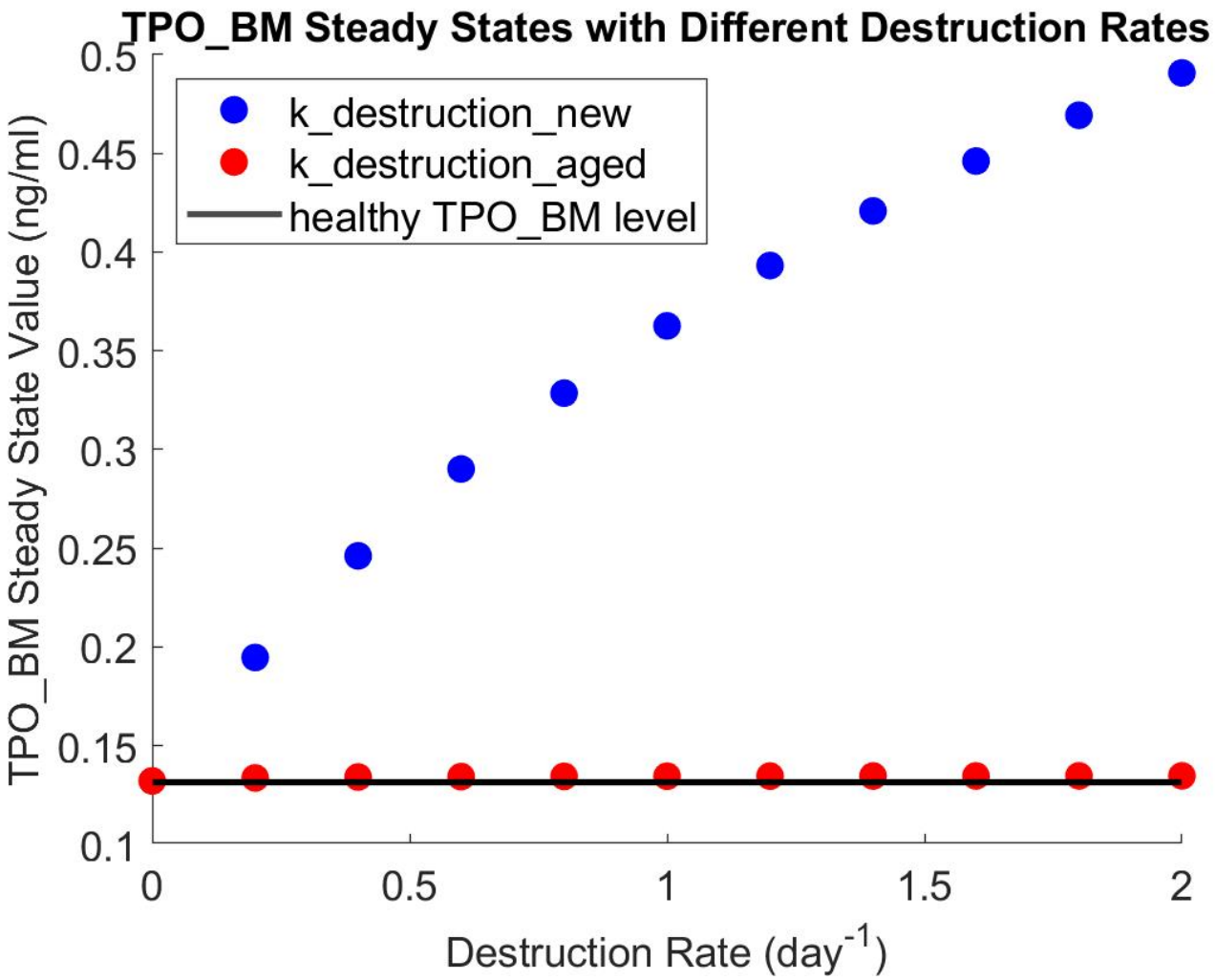
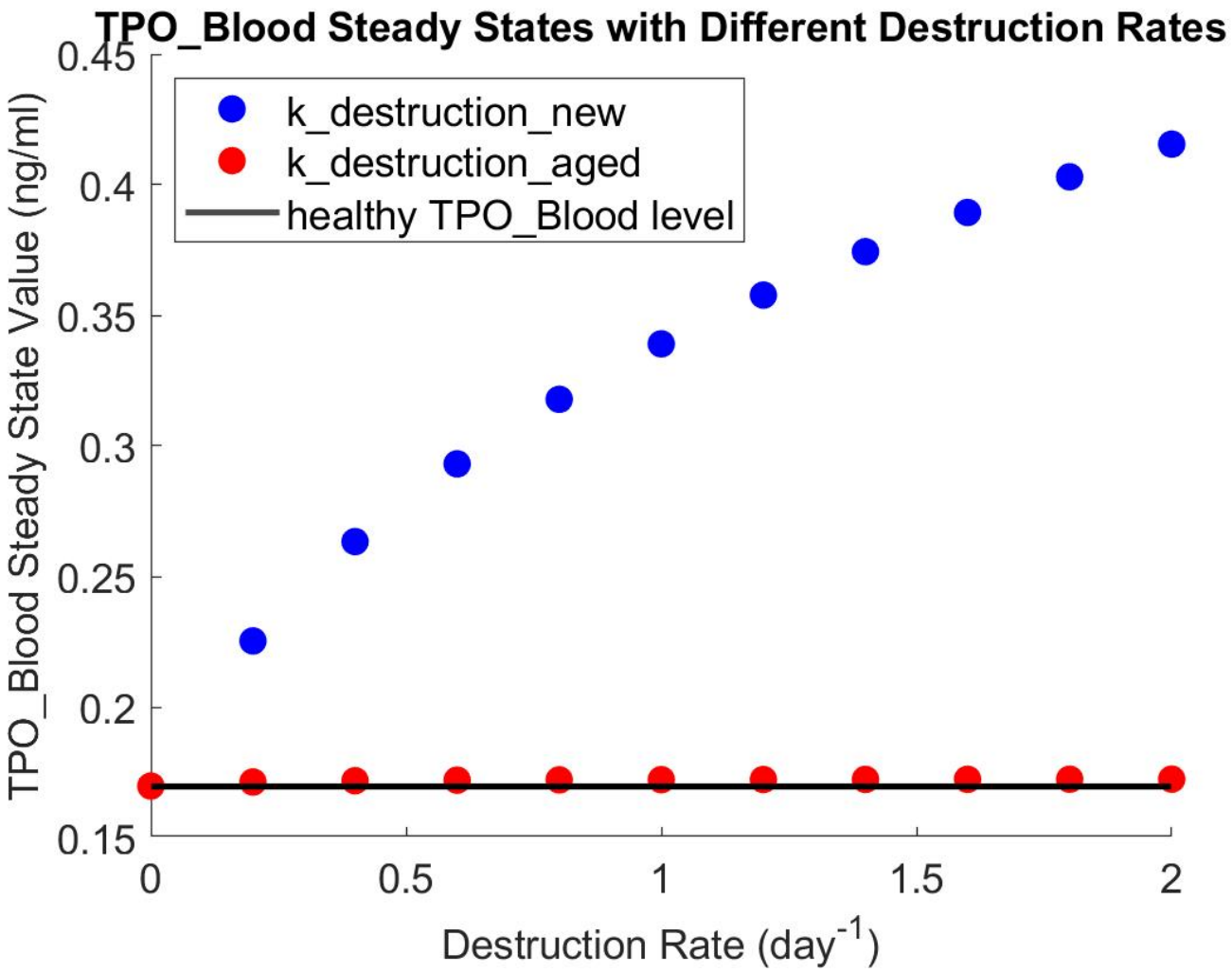


- Healthy TPO_BM: **0.1315 (ng/ml)**

Conclusions

- Clearance of **new platelets** has a **larger impact** on TPO levels in bone marrow than clearance of aged platelets

Results: Individual Destruction Rates

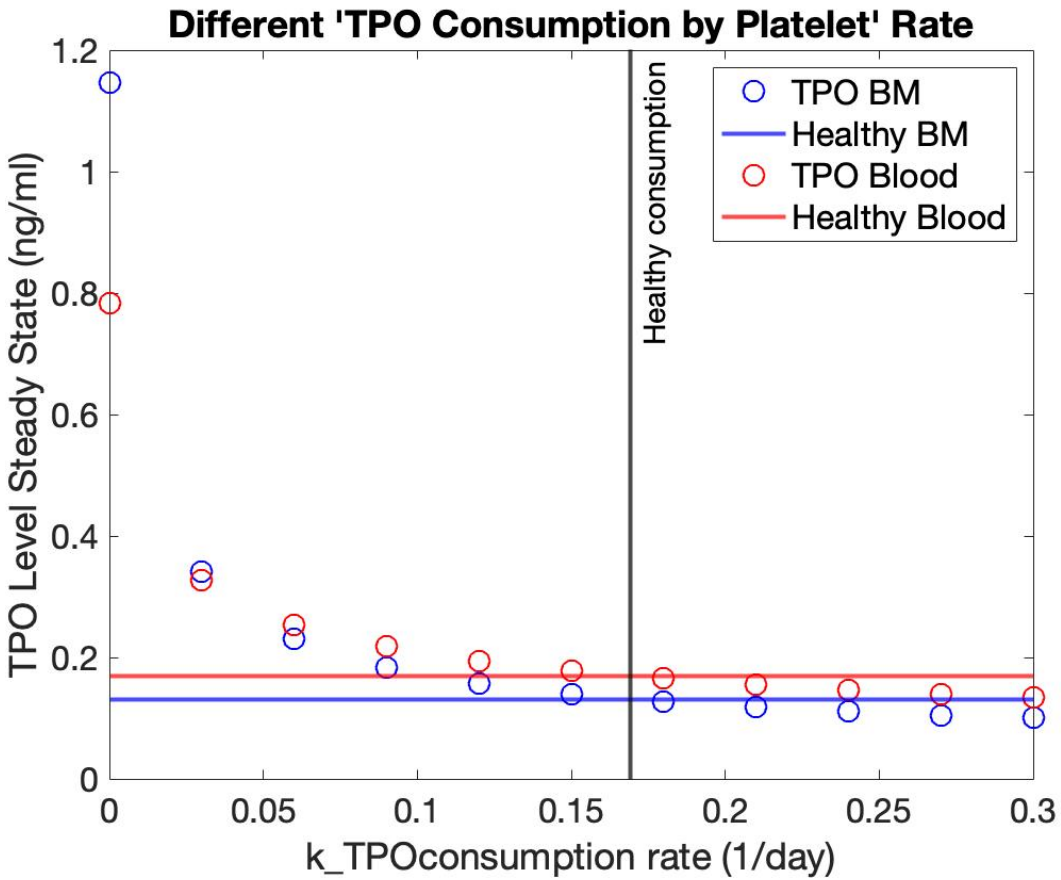


- Healthy TPO_Blood: **0.1698 (ng/ml)**

Conclusions

- Clearance of **new platelets** has a **larger impact** on TPO levels in blood than clearance of aged platelets

Result: k_TPOconsumption and Steady State TPO Levels

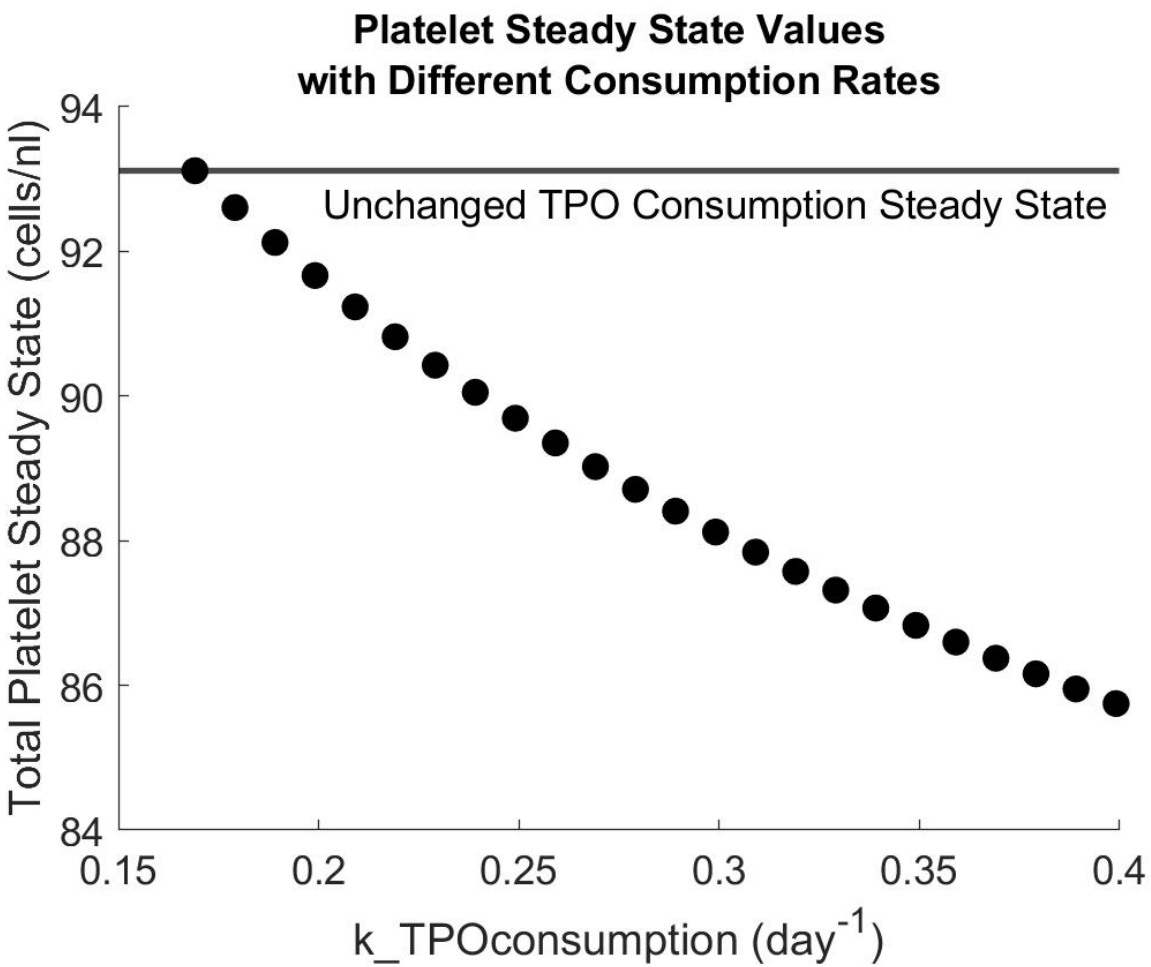


- Healthy k_TPOconsumption: **0.1691 (1/day)**
- Healthy TPO BM Level: **0.1315 (ng/ml)**
- Healthy TPO Blood Level: **0.1698 (ng/ml)**

Conclusion

- **Increasing consumption rate** can help **compensate** for increased TPO levels that result from accelerating platelet destruction

Results: Moderate Platelet Level Case

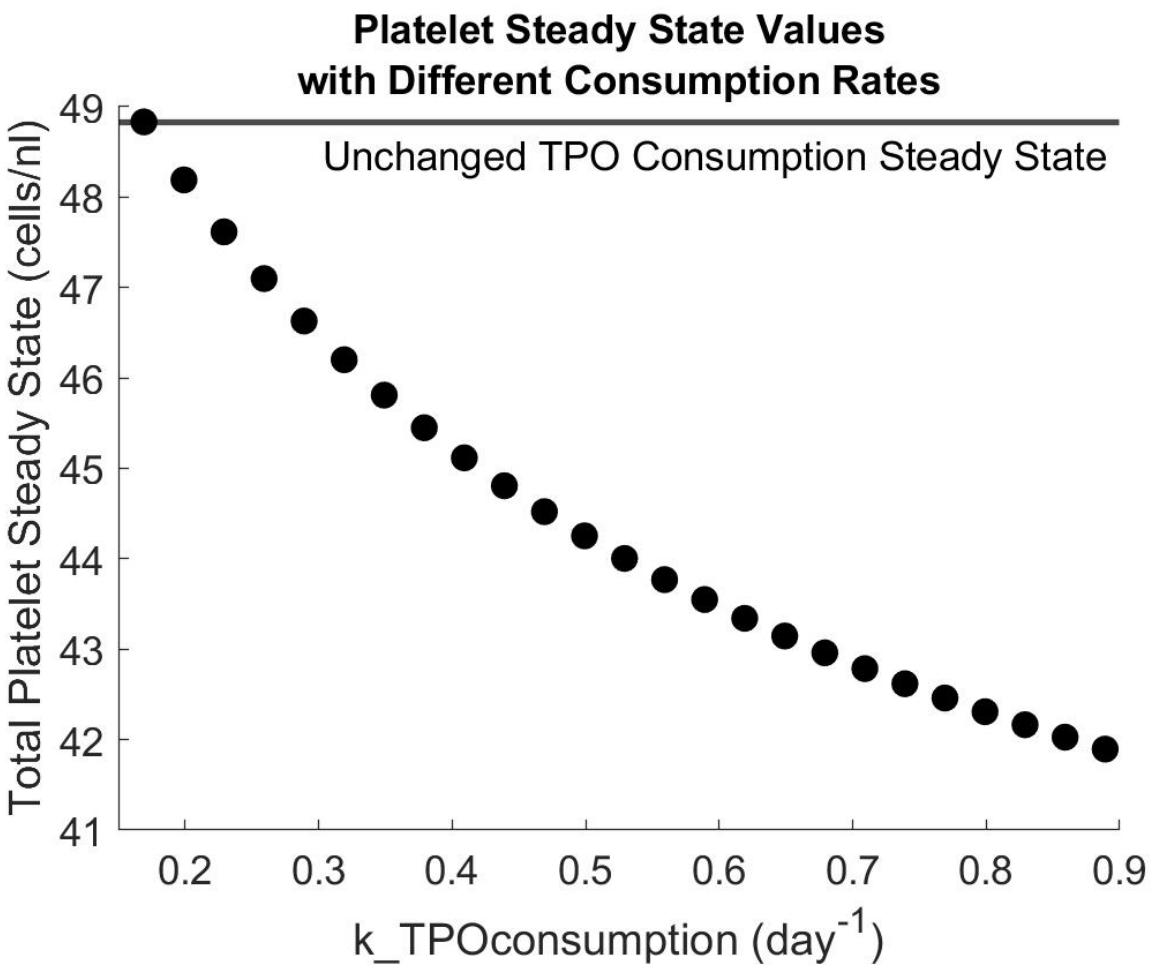


- Baseline k_TPOconsumption: **0.1698 day^{-1}**

Conclusion

- **Increasing TPO consumption** can **decrease** total platelet count by about 10%

Results: Severe Platelet Level Case

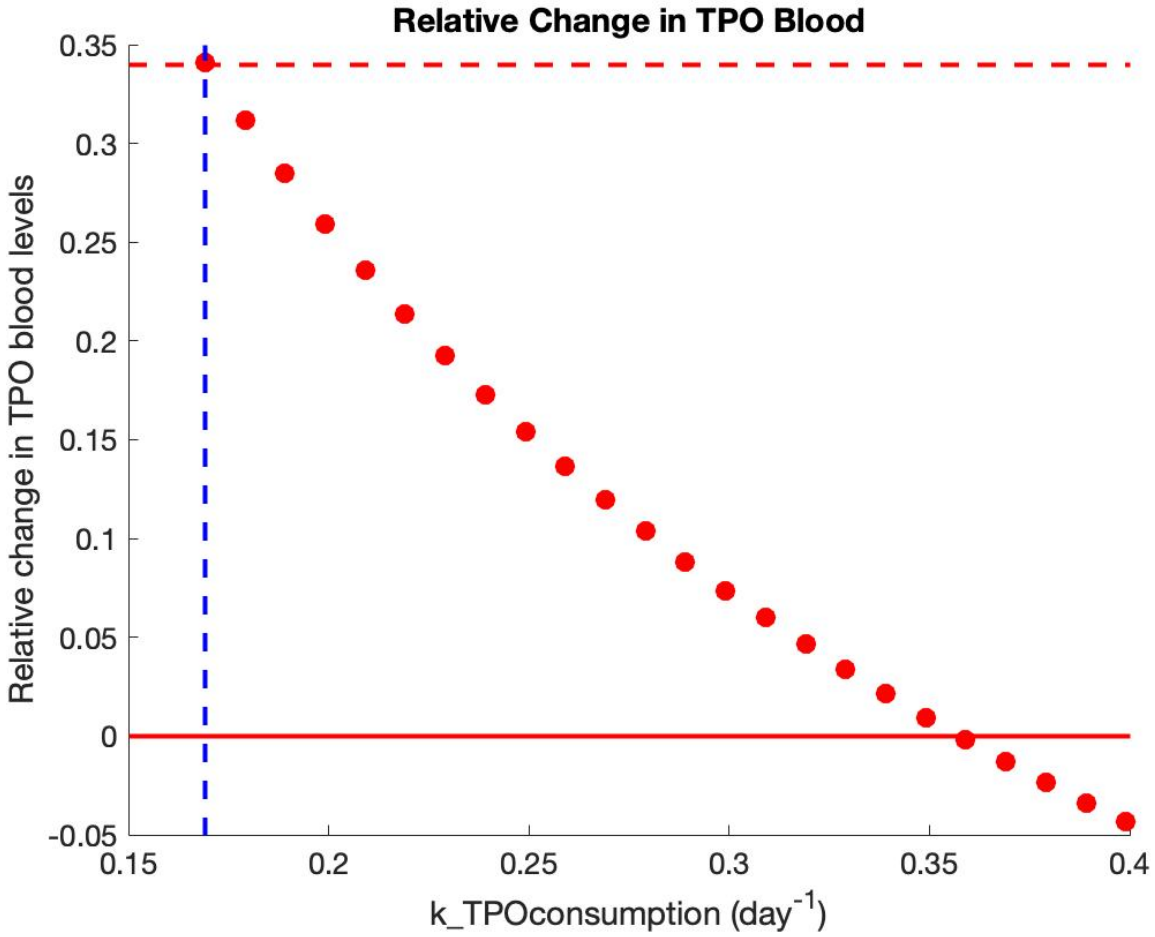


- Baseline k_TPOconsumption: **0.1698 day^{-1}**

Conclusion

- **Increasing TPO consumption** can **decrease** total platelet count by about 17%

Results: Moderate Case



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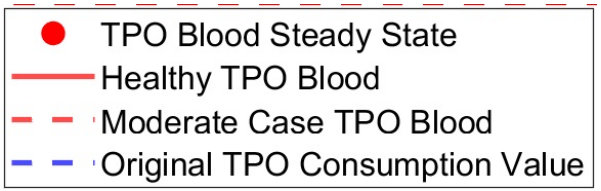
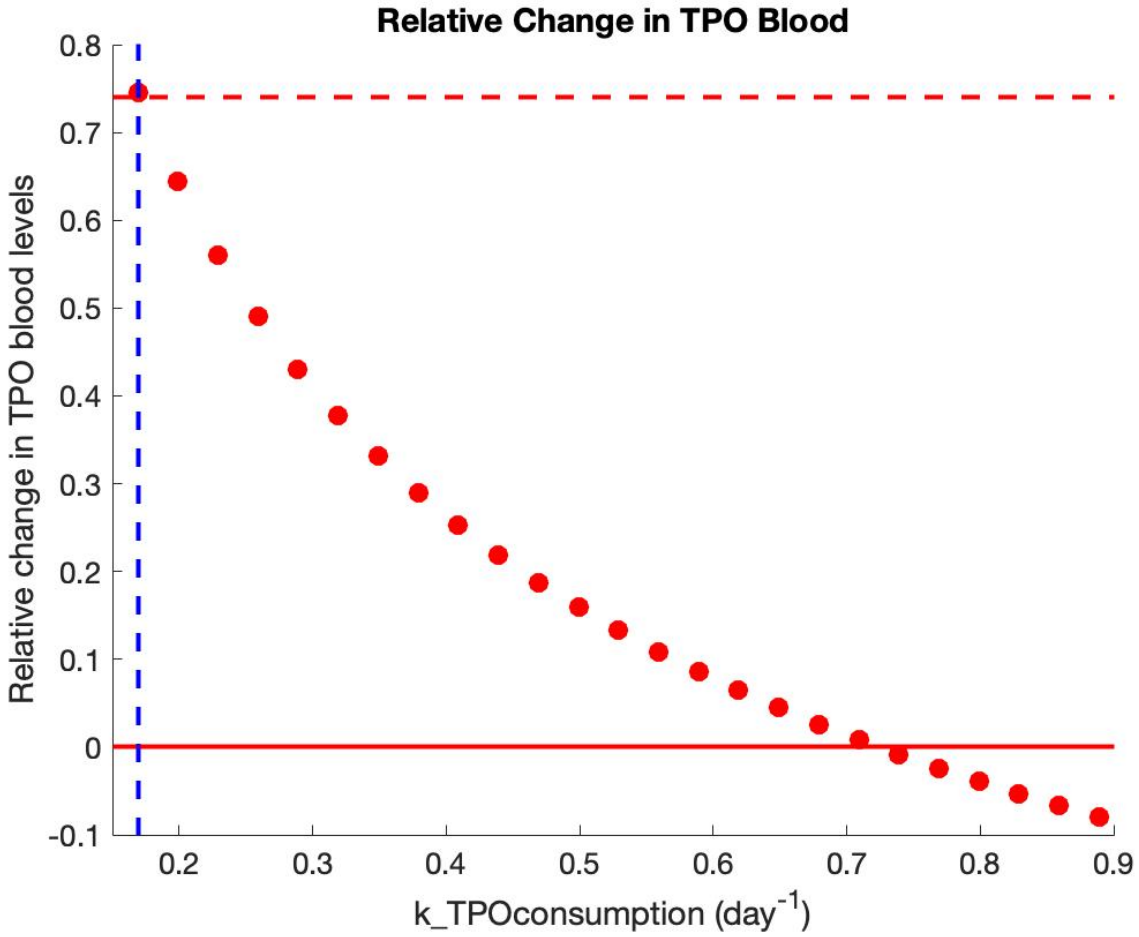


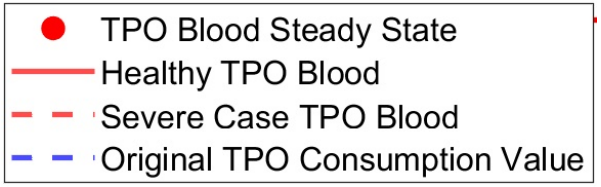
Conclusion

- **Increasing consumption rate** can help **decrease** TPO levels to healthy range

Results: Severe Case



- Healthy Blood TPO: **0.1698 ng/ml**
- k_destruction_aged: **0.4 day^{-1}**
- k_destruction_new: **0.6 day^{-1}**
- Total Platelets: **48 cells/nl**



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