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

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July 17, 2019

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

1. Immune Thrombocytopenia Purpura (ITP)
   - Platelet Production System
   - Immune System
   - Malfunctions in ITP

2. Project Goals

3. Platelet Homeostasis Immune Clearance (PHIC) Model

4. Conclusions
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

Platelet Production System

MB → MB1 → MB2

MK → MK1 → MK2

TPO

Bone Marrow

IL6

TPO

Liver

Blood

P_New → P_Aged

TPO

Affects
Concentration

A → B

MB = Megakaryoblasts
MK = Megakaryocytes
TPO = Thrombopoietin
IL6 = Interukin-6
P = Platelets
Platelet Production System

MB → MB1 → MB2

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MB = Megakaryoblasts
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Affects Concentration

A → B

Blood

P_New → P_Aged

TPO

Blood

Macrophage

Spleen

J. Cerbone and A. Shreeve
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/
Background

Immune Response Malfunction in ITP

Platelets are perceived as pathogens in ITP

Adapted from: https://courses.lumenlearning.com/boundless-ap/chapter/adaptive-immunity/
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 → P_new
P_new → P_aged
P_aged → ø
P_aged → ø
P_aged → ø
P_new → ø

(MK Differentiation into platelets)
(Removal by Liver AMR)
(Immune Clearance)
(Phagocytosis)
(Phagocytosis)

Modified ODEs

\[
\frac{dP_{\text{aged}}}{dt} = \left( (k_{P_{\text{aging}}} \times P_{\text{new}}) - (k_{\text{destruction}_{\text{aged}}} \times P_{\text{aged}}) \right)
- \left( k_{P_{\text{AMR}}} \times \left( \frac{P_{\text{aged}} \times p_1}{P_1 + P_{\text{aged}} \times p_1} \right) \right)
- (k_{P_{\text{immune}}} \times P_{\text{aged}}))
\]

\[
\frac{dP_{\text{new}}}{dt} = \left( -(k_{P_{\text{aging}}} \times P_{\text{new}}) - (k_{\text{destruction}_{\text{new}}} \times P_{\text{new}}) \right)
+ \left( P_{\text{MK}} \times \left( k_{MKd} \times MK2 + E_max \times k_{MKd} \times MK2 \right) \right)
+ \left( \frac{TPO_{BM} \times k_{rate_{diff}_{MK}}}{k_{diff_{MK}} \times m_1 + (TPO_{BM} \times k_{rate_{diff}_{MK}} \times m_1)} \right))
\]
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

- **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 Platelet Destruction Rates

- 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
- TPO\_Blood \rightarrow TPO\_BM
- TPO\_Blood \rightarrow \varnothing \text{(Consumption by platelets)}
- TPO\_BM \rightarrow \varnothing \text{(Consumption by MK)}

ODEs with TPO Change

\[ \frac{dTPO\_Blood}{dt} = \frac{1}{Blood} (\text{Reaction 7} - \text{Reaction 8} - \text{Reaction 15}) \]
\[ \frac{dTPO\_BM}{dt} = \frac{1}{BoneMarrow} (\text{Reaction 8} - \text{Reaction 16}) \]

Reaction 15 Rate

\[ K_{15} = k\_TPO\_consumption \times \left( \frac{(Rate\_k\_TPO\_consumption \times TPO\_Blood)^{h2}}{(k\_plt\_TPO)^{h2} + (Rate\_k\_TPO\_consumption \times TPO\_blood)^{h2}} \right) \times \left( P\_new + (w\_TPO\_consumption \times P\_aged) \right) + d\_TPO \times TPO\_Blood \]
Results: Moderate Case

**Relative Change in TPO Bone Marrow**

- $k_{\text{destruction\_aged}}$: 0.4 day$^{-1}$
- $k_{\text{destruction\_new}}$: 0.2 day$^{-1}$
- Total Platelets: 93 cells/ml

**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**

- \( \text{TPO\_Blood} \rightarrow \text{TPO\_BM} \)  
  (Reaction 8)
- \( \text{TPO\_Blood} \rightarrow \emptyset \)  
  (Consumption by platelets) (Reaction 15)

**ODEs with TPO Change**

\[
\frac{d\text{TPO\_Blood}}{dt} = \frac{1}{\text{Blood}} (\text{Reaction 7} - \text{Reaction 8} - \text{Reaction 15})
\]

\[
\frac{d\text{TPO\_BM}}{dt} = \frac{1}{\text{BoneMarrow}} (\text{Reaction 8} - \text{Reaction 16})
\]

**Reaction Rates**

\[
K_{15} = k_{\text{TPOconsumption}} \times \left( \frac{(\text{Rate}_{k_{\text{TPOconsumption}}} \times \text{TPO\_Blood})^{h_2}}{(k_{plt\_TPO})^{h_2} + (\text{Rate}_{k_{\text{TPOconsumption}}} \times \text{TPO\_blood})^{h_2}} \right) \times (P_{\text{new}} + (w_{\text{TPOconsumption}} \times P_{\text{aged}})) + d_{\text{TPO}} \times \text{TPO\_Blood}
\]

\[
K_8 = k_{\text{TPO1}} \times \text{TPO\_Blood}
\]
Results: Moderate ITP

- $k_{\text{destruction\_aged}} = 0.4 \text{ day}^{-1}$
- $k_{\text{destruction\_new}} = 0.2 \text{ day}^{-1}$

### Adjusted Parameters

#### Original Values (day$^{-1}$)
- $k_{\text{TPO consumption}} = 0.1691$
- $k_{\text{TPO}1} = 0.3123$

#### Adjusted Values (day$^{-1}$)
- $k_{\text{TPO consumption}} = 0.25$
- $k_{\text{TPO}1} = 0.25$

<table>
<thead>
<tr>
<th></th>
<th>TPO Blood</th>
<th></th>
<th>TPO BM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value (ng/ml)</td>
<td>Percent Change</td>
<td>Value (ng/ml)</td>
</tr>
<tr>
<td>Healthy</td>
<td>0.1698</td>
<td>0%</td>
<td>0.1315</td>
</tr>
<tr>
<td>Moderate ITP</td>
<td>0.227</td>
<td>33%</td>
<td>0.1977</td>
</tr>
<tr>
<td>Adjusted Moderate ITP</td>
<td>0.2031</td>
<td>19.6%</td>
<td>0.1253</td>
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</table>

### Conclusion

- To achieve similar results in TPO BM, varying only $k_{\text{TPO consumption}}$, 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

- $k_{\text{destruction\_aged}} = 0.4 \text{ day}^{-1}$
- $k_{\text{destruction\_new}} = 0.6 \text{ day}^{-1}$

**Adjusted Parameters**

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<td>Severe ITP</td>
</tr>
<tr>
<td>0.1698</td>
<td>0%</td>
</tr>
<tr>
<td>0.2963</td>
<td>74%</td>
</tr>
<tr>
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<td>0%</td>
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<tr>
<td>0.2963</td>
<td>74%</td>
</tr>
</tbody>
</table>

**Conclusion**

- To achieve similar results in TPO BM, varying only $k_{\text{TPOconsumption}}$, 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.
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.

We would also like to thank Dr. Simone Cassani, Prof. Suzanne Weekes, Prof. Burt Tilley, and Prof. Stephan Sturm from WPI and Dr. Satyaprakash Nayak, Dr. Sarita Koride, and Matthew Cardinal from Pfizer for their help with this project.

Thank you for your time!
Bibliography


Results: Individual Destruction Rates

Platelet Steady States with Different 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: Individual Destruction Rates

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: $k_{\text{TPO consumption}}$ and Steady State TPO Levels

- **Healthy $k_{\text{TPO consumption}}$:** 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

**Platelet Steady State Values with Different Consumption Rates**

- **Baseline**
  - $k_{TPO consumption}: 0.1698 \text{ day}^{-1}$

**Conclusion**
- Increasing TPO consumption can decrease total platelet count by about 10%
Results: Severe Platelet Level Case

Platelet Steady State Values with Different Consumption Rates

Unchanged TPO Consumption Steady State

Baseline
\( k_{\text{TPO consumption}} : 0.1698 \text{ day}^{-1} \)

Conclusion

- Increasing TPO consumption can decrease total platelet count by about 17%
Results: Moderate Case

Healthy Blood TPO: 0.1698 ng/ml
k_destruction_aged: 0.4 day\(^{-1}\)
k_destruction_new: 0.2 day\(^{-1}\)
Total Platelets: 93 cells/ml

**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/ml

Conclusion

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