Stability of Control System of Intracellular Iron Homeostasis: A Mathematical Proof

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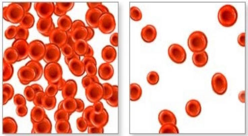
Blood Donor Eligibility

- Frequently asked questions
  - Age
  - Weight
  - Medical History
- Hemoglobin Levels
  - Red blood cells

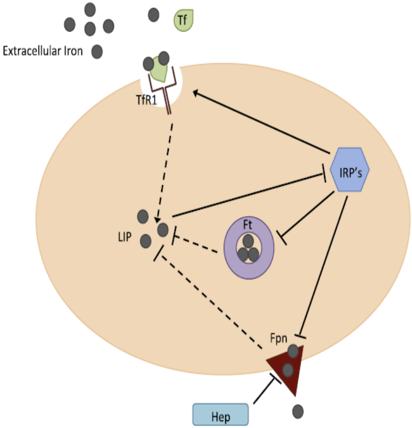
Background

- Importance of iron in the blood cells
  - Essential for cellular metabolism
  - The levels are tightly constrained



- "The core control system of intracellular iron homeostasis: A Mathematical model" [1]
  - Principal paper that presents the mathematical model of the control system

Chifman *et al.* Model



- The solid lines indicate positive or negative regulation.
- The dotted line are reactions that consume or produce the indicated species.

The ODE's that define the mathematical model

- The x_i with $i \in \{1, \ldots, 5\}$ is an activating/inhibiting state variable.

$$\dot{x_1} = \alpha_1 Fe_{ex} x_2 + \gamma_4 x_4 - \alpha_6 x_1 x_3 - \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5},$$

$$\dot{x_2} = \alpha_2 \frac{x_5}{k_{52} + x_5} - \gamma_2 x_2,$$

$$\dot{x_3} = \alpha_3 \frac{k_{53}}{k_{53} + x_5} - (\gamma_3 + \gamma_h Hep) x_3,$$

$$\dot{x_4} = \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5} - \gamma_4 x_4,$$

$$\dot{x_5} = \alpha_5 \frac{k_{15}}{k_{15} + x_1} - \gamma_5 x_5.$$

The ODE's that define the mathematical model

- The k_{nj} is the activation threshold for $n \in \{1, 5\}$ and $j \in \{2, 3, 4, 5\}$.

$$\dot{x_1} = \alpha_1 Fe_{ex} x_2 + \gamma_4 x_4 - \alpha_6 x_1 x_3 - \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5},$$

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The ODE's that define the mathematical model

- The α_ℓ is the maximum production rate of the regulated protein for $\ell \in \{1, \ldots, 6\}$

$$
\begin{aligned}
\dot{x_1} &= \alpha_1 Fe_{ex} x_2 + \gamma_4 x_4 - \alpha_6 x_1 x_3 - \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5}, \\
\dot{x_2} &= \alpha_2 \frac{x_5}{k_{52} + x_5} - \gamma_2 x_2, \\
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\dot{x_5} &= \alpha_5 \frac{k_{15}}{k_{15} + x_1} - \gamma_5 x_5.
\end{aligned}
$$

The ODE's that define the mathematical model

- Each protein undergoes self-degradation, thus each protein has a decay rate γ_j.

$$\dot{x_1} = \alpha_1 Fe_{ex} x_2 + \gamma_4 x_4 - \alpha_6 x_1 x_3 - \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5},$$

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The ODE's that define the mathematical model

- *Hep* and Fe_{ex} are control parameters, so they are considered constants fixed between 0 and 1.

$$\dot{x_1} = \alpha_1 Fe_{ex} x_2 + \gamma_4 x_4 - \alpha_6 x_1 x_3 - \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5},$$
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Steady state of the system

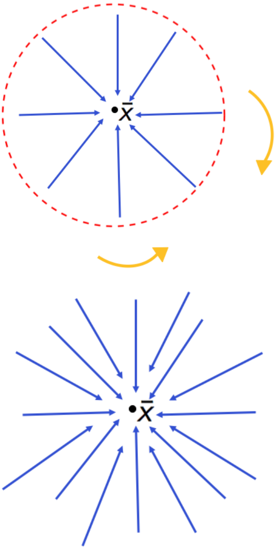
- This system has a unique solution which is:

$$P(x_1) = ax_1^3 + bx_1^2 \pm cx_1 - d = 0$$

where a, b, c and d > 0, where

$$a = \alpha_3\alpha_6\gamma_2(\gamma_5^2)k_{52}k_{53},$$
$$b = \alpha_3\alpha_6\gamma_2\gamma_5 k_{15}k_{53}(\alpha_5 + 2\gamma_5 k_{52}),$$
$$c = \gamma_5 k_{15}(-\alpha_1\alpha_2\alpha_5 \mathrm{Fe}_{\mathrm{ex}}(\gamma_3 + \hat{\gamma}_h \mathrm{Hep}) + \alpha_3\alpha_6\gamma_2 k_{15}(\alpha_5 + \gamma_5 k_{52}))k_{53},$$
$$d = -\alpha_1\alpha_2\alpha_5 Fe_{ex}(\gamma_3 + \hat{\gamma}_h \mathrm{Hep})(k_{15})^2(\alpha_5 + \gamma_5 k_{53}).$$

Stability of a system



1. Locally Stable
2. Globally Stable
3. Unstable

The Proposal

GOAL

Prove or disprove mathematically the global stability of $\dot{x} = (\dot{x_1}, \ldots, \dot{x_5})$ for all initial conditions $x(0) = (x_1(0), \ldots, x_5(0)) \in \mathbb{R}^5_{>0}$.

In other words, I want to prove that

$$\lim_{t \to \infty} x(t) = \bar{x}.$$

Proving Local Stability

- The main goal of Chifman *et al.* was proving local stability
- First approach: Prove local stability

Methods for Local Stability

Jacobian Matrix and Eigenvalues

With the Jacobian matrix of the system we find the eigenvalues by using the characteristic equation:

$$det(J - \lambda I).$$

If all the eigenvalues have negative real part, then the system is locally stable.

Hurwitz Matrix

Given a real polynomial

$$\mathcal{P}(\lambda) = a_0\lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n,$$

the $n \times n$ square matrix

$$H_n = \begin{pmatrix} a_1 & a_3 & a_5 & \dots & 0 & 0 \\ a_0 & a_2 & a_4 & \dots & 0 & 0 \\ 0 & a_1 & a_3 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & a_{n-1} & 0 \\ 0 & 0 & 0 & \dots & a_{n-2} & a_n \end{pmatrix}$$

is called the *Hurwitz matrix* corresponding to the polynomial $\mathcal{P}(\lambda)$.

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Methods for Local Stability

Routh-Hurwitz criterion

For an n-degree polynomial

$$\mathcal{P}(\lambda) = a_0\lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n,$$

where $a_i, i = 0, 1, ...n$ are all real, we define n Hurwitz matrices. All the roots of the polynomial have negative real part if and only if the determinants of the Hurwitz matrices are positive.

Simplifying the System

- The system with 5 ODE's is computationally challenging because of all the unknown parameters.
- We must simplify the system in a way that is biologically possible.
- Talked with Dr.Paul Lindahl on ways to simplify the system.

The original mathematical model

- In the original model we have proteins that help with iron import and export

$$
\begin{aligned}
\dot{x}_1 &= \alpha_1 Fe_{ex} x_2 + \gamma_4 x_4 - \alpha_6 x_1 x_3 - \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5}, \\
\dot{x}_2 &= \alpha_2 \frac{x_5}{k_{52} + x_5} - \gamma_2 x_2, \leftarrow \text{Iron import} \\
\dot{x}_3 &= \alpha_3 \frac{k_{53}}{k_{53} + x_5} - (\gamma_3 + \gamma_h Hep) x_3, \leftarrow \text{Iron export} \\
\dot{x}_4 &= \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5} - \gamma_4 x_4, \\
\dot{x}_5 &= \alpha_5 \frac{k_{15}}{k_{15} + x_1} - \gamma_5 x_5.
\end{aligned}
$$

Simplifying the Model

- The model also has rates that represent the iron import and iron export

$$\dot{x_1} = \alpha_1 Fe_{ex} x_2 + \gamma_4 x_4 - \alpha_6 x_1 x_3 - \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5}$$

where α_1 is iron import and α_6 is iron export.

- We make x_2 and x_3 constants and combine them with their respective rates,

$$\dot{x_1} = \alpha_1 Fe_{ex} x_2 + \gamma_4 x_4 - \alpha_6 x_1 x_3 - \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5}.$$

The simplified model

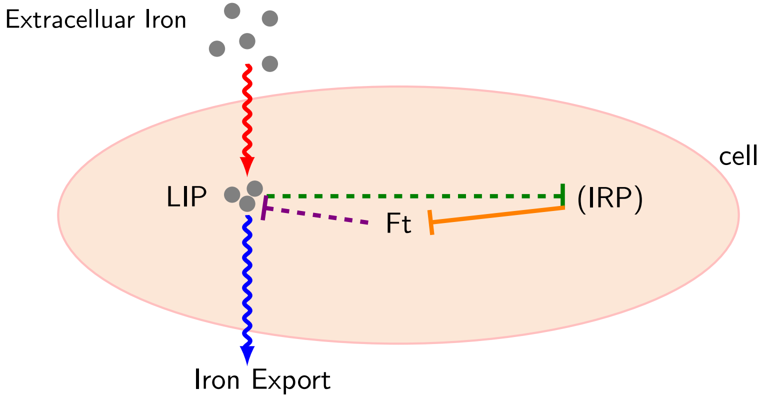
- Now, the new iron import rate is $\hat{\alpha_1} = \alpha_1 x_2$ and the new iron export rate is $\hat{\alpha_6} = \alpha_6 x_3$. Thus the new simplified model is:

$$\dot{x_1} = \hat{\alpha_1} \mathrm{Fe}_{\mathrm{ex}} + \gamma_4 x_4 - \hat{\alpha_6} x_1 - \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5}$$

$$\dot{x_4} = \alpha_4 x_1 \frac{k_{54}}{k_{54} + x_5} - \gamma_4 x_4$$

$$\dot{x_5} = \alpha_5 \frac{k_{15}}{k_{15} + x_1} - \gamma_5 x_5.$$

The resulting control system



Steady state of the simplified model

- For any choice of parameters, the simplified model has the following unique steady state:

$$\bar{x}_1 = \frac{\hat{\alpha}_1 \mathsf{Fe}_{\mathsf{ex}}}{\hat{\alpha}_6},$$

$$\bar{x}_4 = \frac{\mathsf{Fe}_{\mathsf{ex}}^2 \alpha_4 \gamma_5 k_{54} \hat{\alpha}_1{}^2 + \mathsf{Fe}_{\mathsf{ex}} \alpha_4 \gamma_5 k_{15} k_{54} \hat{\alpha}_1 \hat{\alpha}_6}{\mathsf{Fe}_{\mathsf{ex}} \gamma_4 \gamma_5 k_{54} \hat{\alpha}_1 \hat{\alpha}_6 + (\gamma_4 \gamma_5 k_{15} k_{54} + \alpha_5 \gamma_4 k_{15}) \hat{\alpha}_6{}^2},$$

$$\bar{x}_5 = \frac{\alpha_5 k_{15} \hat{\alpha}_6}{\mathsf{Fe}_{\mathsf{ex}} \gamma_5 \hat{\alpha}_1 + \gamma_5 k_{15} \hat{\alpha}_6}.$$

Local stability of simplified system

Theorem (Eithun and M)

The simplified system has a unique steady state and it is locally stable.

1. Verify that the coefficients of the characteristic polynomial of the Jacobian matrix are all positive.
2. Next, we need to verify that the principal minors $\Delta_1, \Delta_2, \Delta_3$ of the Hurwitz matrix are positive.
3. By using the Routh-Hurwitz criterion the eigenvalues are all negative, thus proving that the steady state is locally stable. $\square$

Geometric Analysis

(Loading Video...)

- Vector fields of our system
  - $\dot{x}_1 = 0$ is the blue surface
  - $\dot{x}_4 = 0$ is the orange surface
  - $\dot{x}_5 = 0$ is the red surface.

Geometric Analysis

Example ($\dot{x}_1 + \dot{x}_4$)

First, if we look at the system we notice that

$$\dot{x}_1 + \dot{x}_4 = \hat{\alpha}_1 \mathrm{Fe}_{\mathrm{ex}} - \hat{\alpha}_6 x_1.$$

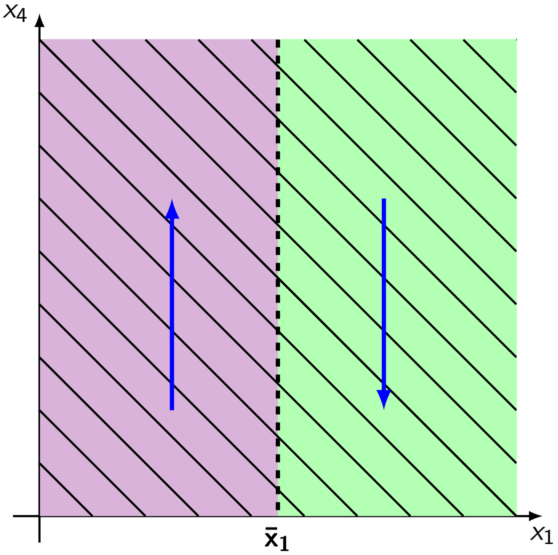
We consider the case: $\mathbf{x_1} < \bar{\mathbf{x}}_\mathbf{1}$

Let $\bar{x}_1 = \dfrac{\hat{\alpha}_1 \mathrm{Fe}_{\mathrm{ex}}}{\hat{\alpha}_6}$, then

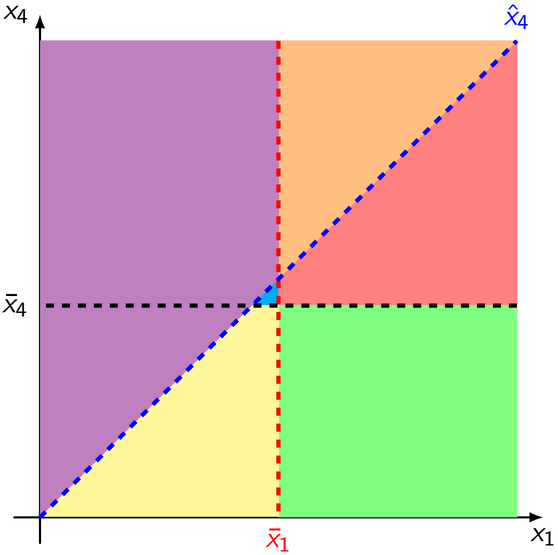
$$\dot{x}_1 + \dot{x}_4 > \hat{\alpha}_1 \mathrm{Fe}_{\mathrm{ex}} - \hat{\alpha}_6 x_1 > \hat{\alpha}_1 \mathrm{Fe}_{\mathrm{ex}} - \hat{\alpha}_6 \bar{x}_1 = 0$$

Therefore, $\dot{x}_1 + \dot{x}_4 > 0$. If we look at $\mathbf{x_1} > \bar{\mathbf{x}}_\mathbf{1}$, then $\dot{x}_1 + \dot{x}_4 < 0$.

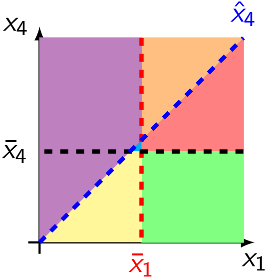
Geometric Analysis



The Six Regions



Behavior of equations in the six regions



Color of region	Behavior of equations in the region
(purple)	$\dot{x}_1 + \dot{x}_4 > 0$ & $\dot{x}_4 < 0$ & $\dot{x}_1 > 0$
(yellow)	$\dot{x}_1 + \dot{x}_4 > 0$ & If $x_5 < \bar{x}_5$, then $\dot{x}_5 > 0$
(blue)	$\dot{x}_5 > 0, \dot{x}_4 < 0$, and $\dot{x}_1 > 0$. This region exists iff $x_5 < \bar{x}_5$
(orange)	$\dot{x}_1 + \dot{x}_4 < 0$ & $\dot{x}_4 < 0$
(red)	$\dot{x}_1 + \dot{x}_4 < 0$ & If $x_5 > \bar{x}_5$, then $\dot{x}_5 < 0$
(green)	$\dot{x}_1 + \dot{x}_4 < 0$ & If $x_5 > \bar{x}_5$, then $\dot{x}_5 < 0$. Otherwise, $\dot{x}_4 > 0$ and $\dot{x}_1 < 0$

What does this tell us about the Global Stability?

- Our goal is to get to our steady state.
- By looking at the behavior of the equations in a region, we notice we are getting closer to the steady state.
- The system seems to be globally stable, but a few details remain to be worked out.

Summary

- For a valid approximation of the Chifman *et al.* model, we showed that it has a steady state and it is locally stable.
- We also show that this model points toward global stability by using a geometric analysis.
- All of this may point to a proof for the local and global stability of the Chifman *et al.* model.

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Thank you.

References

[1] J. Chifman, A. Kniss, P. Neupane, I. Williams, B. Leung, Z. Deng, P. Mendes, V. Hower, F.M. Torti, S.A. Akman, S.V. Torti, R. Laubenbacher, The core control system of intracellular iron homeostasis: A mathematical model,*Journal of Theoretical Biology, Volume 300, 7 May 2012, Pages 91-99, ISSN 0022-5193, http://dx.doi.org/10.1016/j.jtbi.2012.01.024.*