A Model of Iron Metabolism in the Human Body

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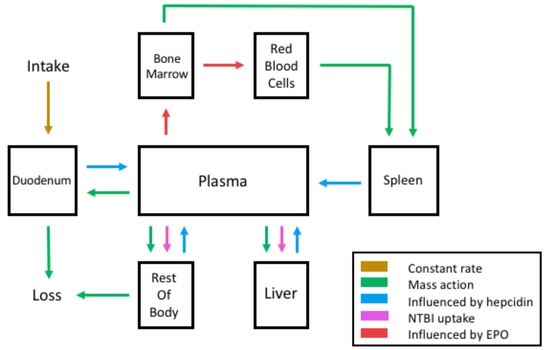
Introduction

- Iron-related diseases are prevalent throughout the world.
- Anemia affects one quarter of the world's population.
- Hemochromatosis, a disease of iron overload, is the most common inherited disease of gene mutation in Caucasians.
- Understanding the mechanisms of iron metabolism will advance progress towards individualized treatment strategies.
- A mathematical model using ordinary differential equations (ODE) is developed to simulate iron distribution in the major organs of the body.
- This model is based on previous work modeling iron metabolism in mice [6].

Model



- The model consists of 7 compartments and 23 equations, which describe the flow of iron between compartments, the irreversible binding of iron to transferrin in the plasma, and the synthesis and degradation of key regulatory proteins hepcidin and erythropoetin (EPO).
- Iron enters the body through dietary intake and leaves through intestinal cell shedding (represented as loss from the duodenum) and through hair, sweat, and dead skin (represented as loss from the rest of body).
- As an example of the form of an ODE in the model, the equation that governs iron flux in the spleen is

$$\frac{d[FeSpleen] \cdot V_{Spleen}}{dt} = (kRBCSpleen \cdot [FeRBC] \cdot V_{RBC}) + (kBMSpleen \cdot [FeBM] \cdot V_{BoneMarrow}) - \left(\frac{VSpleenNTBI \cdot V_{Spleen} \cdot [FeSpleen]}{(Km + [FeSpleen]) \cdot (1 + \frac{[Hepcidin]}{Ki})}\right)$$

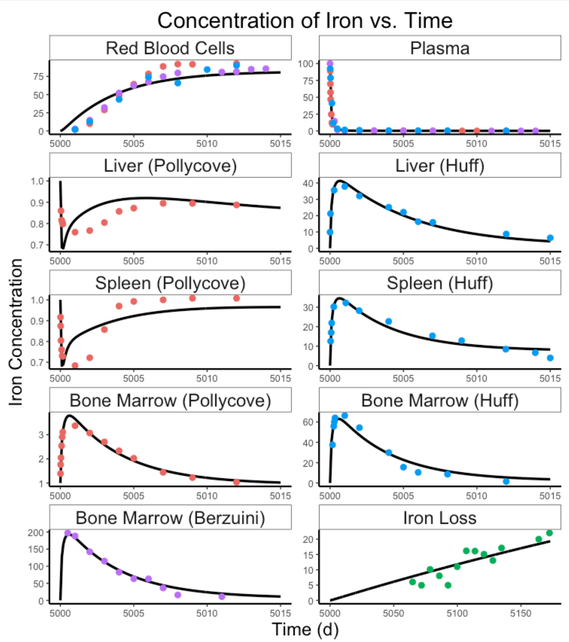
Methods

- Some parameter values, including the volume and iron concentration of the organs, were obtained from literature.
- The remainder were estimated using experimental data from subjects injected with radioactive iron [1-3, 5, 7].
- Parameter sets were generated by minimizing an objective function (sum of squared residuals) using a variety of optimization algorithms.
- The chosen parameter set was required (1) to produce a small objective value, and (2) to render the following quantities close to biologically realistic ranges:

Total Iron	Percent Iron in RBC	Transferrin Saturation
2 – 5 g	60 – 75%	24 – 40%

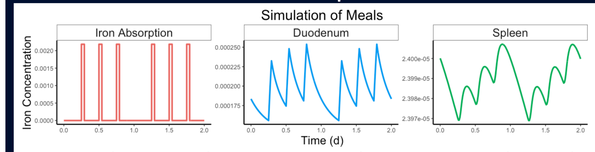
- Parameter estimates were carried out using the software COPASI, a biochemical system simulator [4].

Model Calibration

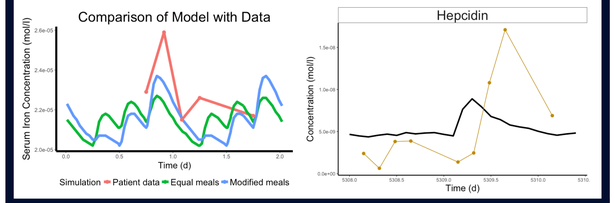


Total Iron	Percent Iron in RBC	Transferrin Saturation
3.5 g	84.1%	35.3%

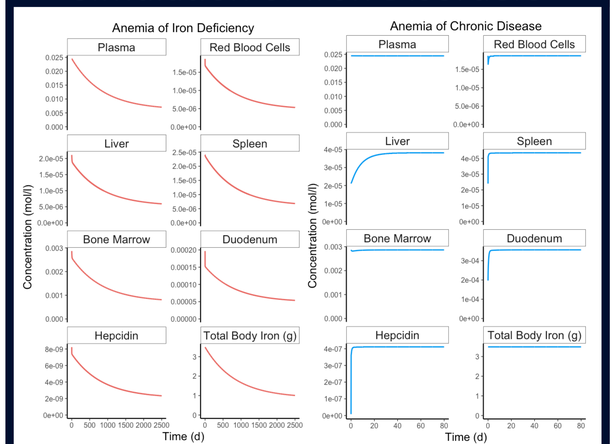
Addition of Hepcidin Data



- To replicate meal patterns, iron absorption was changed from a continuous rate to a sequence of discrete events.
- The results of meal simulations align closely with time course data of serum iron [3], and allow estimation of parameters related to hepcidin.
- Once the model was aligned, the hepcidin data was included in the model calibration.



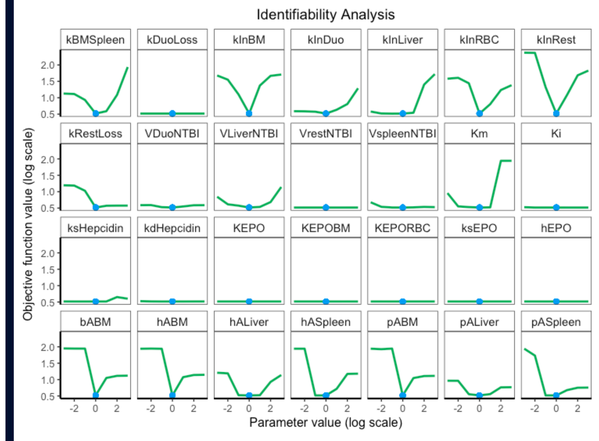
Simulation of Iron Disorders



- Iron deficiency anemia is the result of insufficient iron in the diet.
- When infected with a pathogen, the body increases hepcidin production so as to decrease iron concentration in the blood. Anemia of chronic disease results when this response is sustained over an extended period of time.
- Simulations of iron deficiency anemia and anemia of chronic disease broadly reflect these pathologies.

Parameter Identifiability

- Identifiability analysis is a tool used to ascertain the extent to which estimated parameters are determined by data.



- The values of parameters for which data was available (e.g., KEPO) are more certain than those for which data was not available (e.g., kInBM).

Discussion

- The model is capable of fitting data from multiple individuals, and accurately simulates anemia and the effect of meals.
- As relevant data is added, parameter identifiability will improve.
- With the availability of individual data, this model could be personalized for use in precision medicine.
- For example, an individual's weight, height, and age could be used to estimate organ volumes and iron concentrations.

References

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