Whole Body Model of Iron Dynamics

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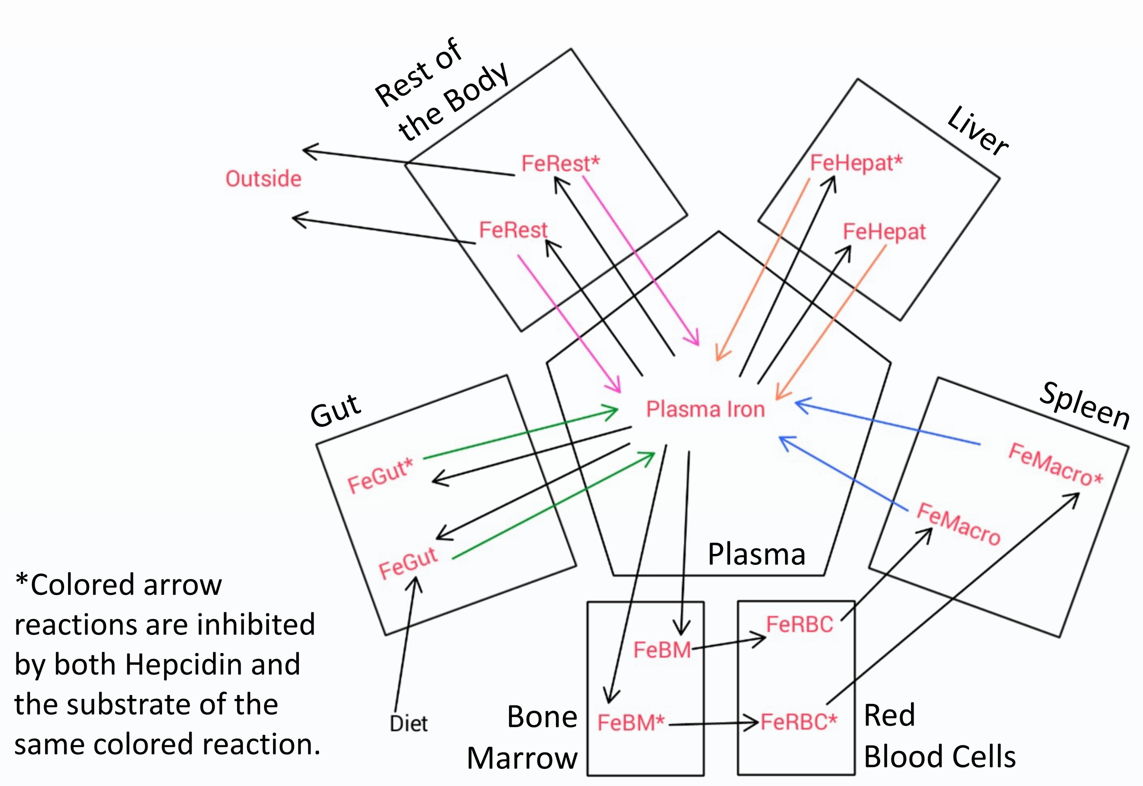
Aims

- Create a model for iron metabolism that is:
    - Predictive
    - Compartmental
    - Able to track all iron in the body
- Simulate a variety of diets and iron metabolism disorders

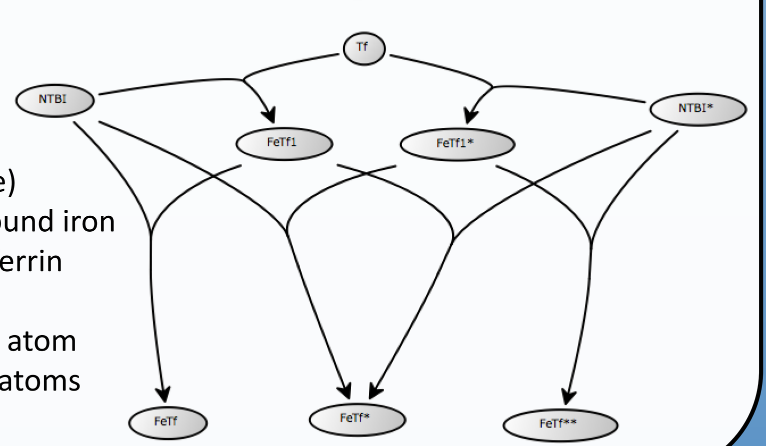
Model Diagram



*Colored arrow reactions are inhibited by both Hepcidin and the substrate of the same colored reaction.

Plasma Iron Diagram

- Tf – Transferrin (Iron Carrier Molecule)
- NTBI - Non-transferrin bound iron
- FeTf1 - Monoferric transferrin
- FeTf - Diferric transferrin
- * - single radioactive iron atom
- ** - two radioactive iron atoms



Future work

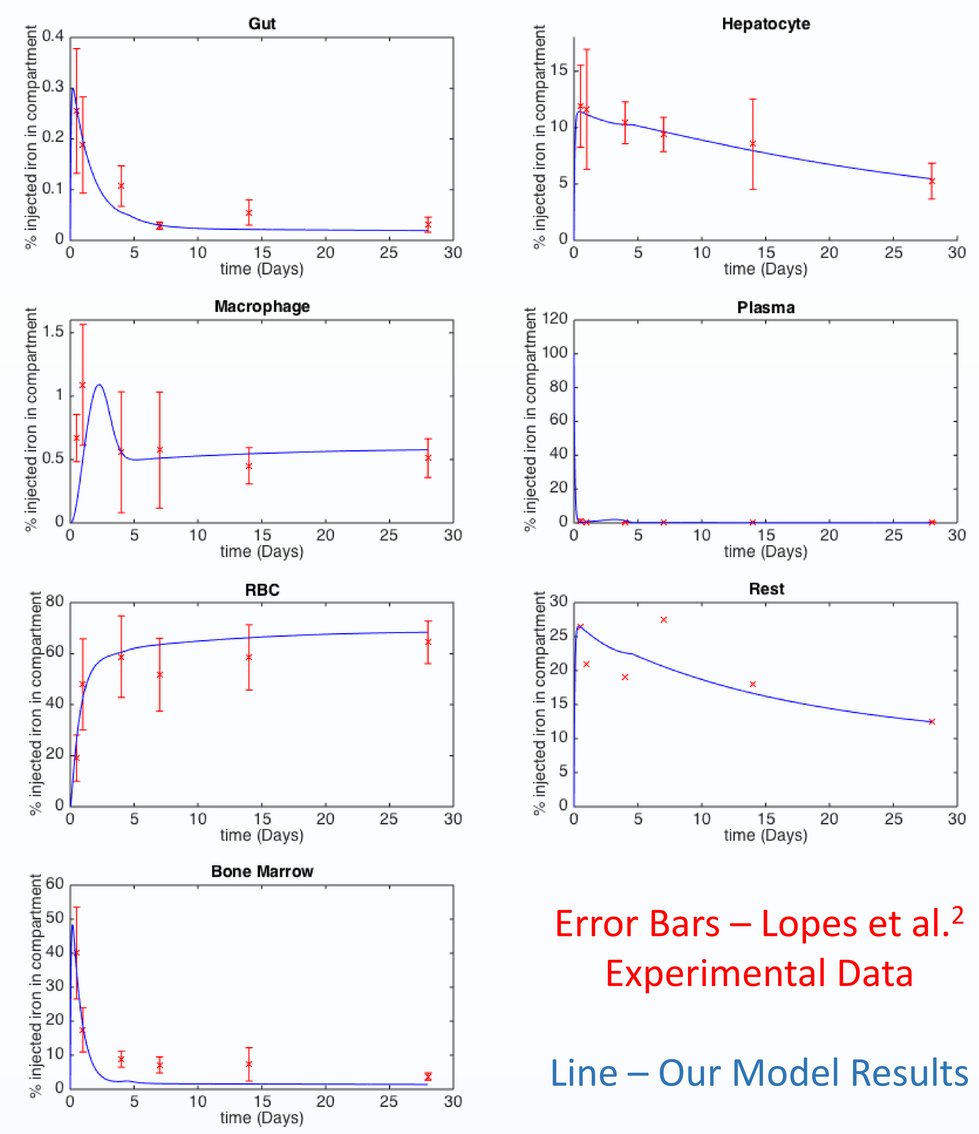
- Calibrate model with variable Hepcidin
    - Add Ferritin iron storage within cells
- Scale Mouse model up to human model
- Run simulations on human model for diet and iron disorders
- Add cellular level detail
- Validation

Abstract

Iron plays an important role in many processes of the body, most importantly oxygen transport by red blood cells. The goal of this research is to create a predictive model of whole body iron metabolism for humans. As a first step, a whole body model of iron homeostasis was created for mice. This model will be used to gain a better understanding of iron metabolism disorders (i.e. anemia and hemochromatosis). The present mouse model was calibrated to data previously published by the Reich group. All calculations, including parameter estimation, were carried out with the open-source software COPASI[1].

Results

Best Fit of Adequate Iron Diet Experimental Data



Error Bars – Lopes et al.[2] Experimental Data

Line – Our Model Results

Steady State Ratios of Adjusted / Normal Hepcidin

Iron Species	Normal Hepcidin	20% of Normal (Lower Hepcidin) Hemochromatosis	180% of Normal (Higher Hepcidin) Anemia
GUT	1	0.192	2.17
RED BLOOD CELLS	1	3.79	0.684
MACROPHAGES	1	0.746	1.27
HEPATOCYTES	1	0.761	1.25
TRANSFERRIN	1	0.151	1.12
HEPCIDIN	1	0.2	1.8
FeTf	1	5.7	0.577
FeTf1	1	0.3	0.879
NTBI	1	19	0.656
REST OF THE BODY	1	1	1
BONE MARROW	1	3.79	0.684
TOTAL BODY IRON	1	3.31	0.754
Tf SATURATION	1	3.79	0.684
PLASMA IRON	1	3.79	0.684

Red indicates unexpected Results

	Hemochromatosis		Anemia	
	Increase	Decrease	Increase	Decrease
Expectations	NTBI Transferrin Saturation Total Body Iron FeGut FeMacro FeHepat Plasma Iron	Transferrin	FeGut FeHepat FeMacro Transferrin	RBC Total Body Iron Transferrin Saturation NTBI Plasma Iron

Sensitivity Analysis

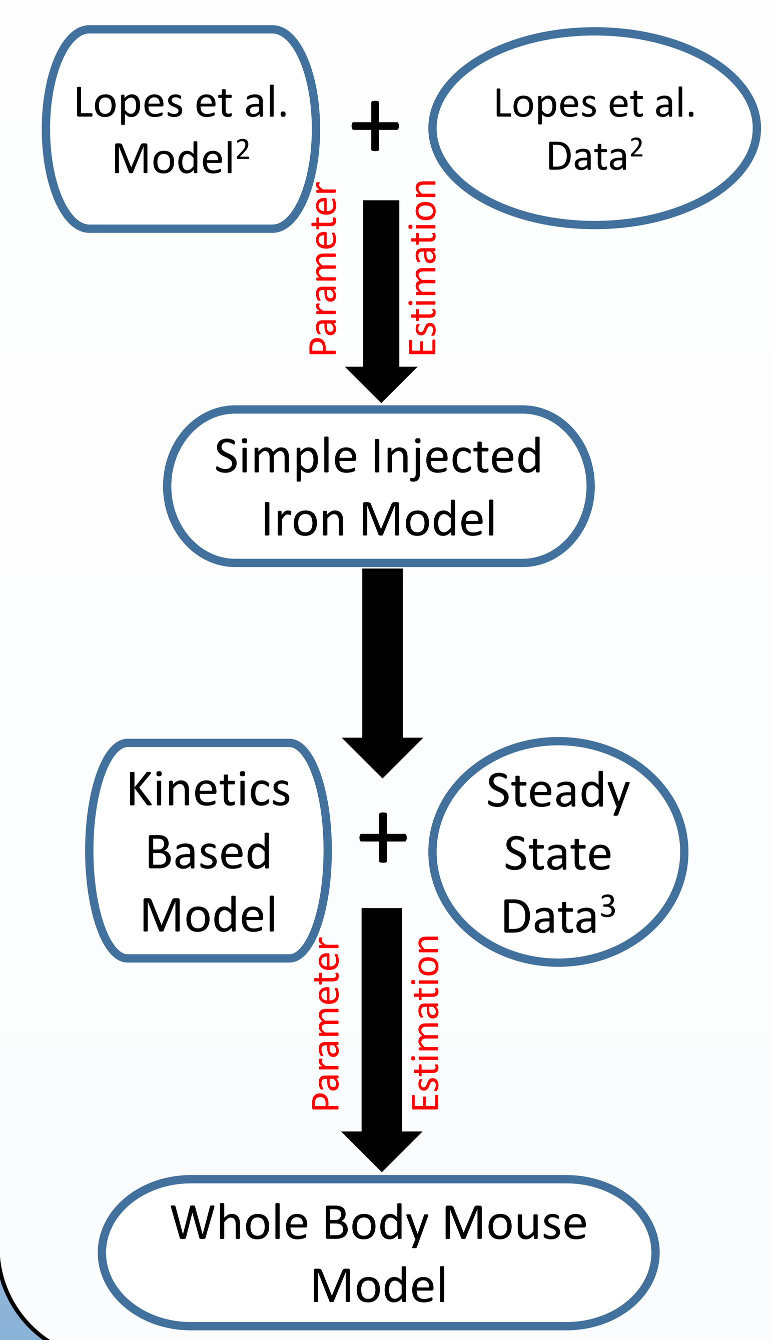
Sensitivity analysis included two unexpected results:

1. The rate constant (kInRBC) for the Bone Marrow -> Red Blood Cells reaction has no effect on the steady state iron concentration in RBCs, but does decrease the iron concentration in Bone Marrow
2. Rate constants for iron entering and leaving the rest of the body have a strong influence on nearly all other iron species

	kNTBI_FeTf1	kInGut	kInHepat	kInRBC	kInRest	Km	Ki	kFeTf1_FeTf	VgutNTBI
FeGut	0	0.051977	0	0	-0.0519244	0.963331	-1.179850	0	-1.234690
FeRBC	7.16E-13	-3.76E-12	-1.79E-12	-5.37E-13	-0.999001	-0.704779	0.709476	1.79E-12	-1.43E-12
FeMacro	7.86E-13	-3.93E-12	-1.77E-12	-1.96E-13	-1.148330	0.189023	-0.325525	1.77E-12	-1.57E-12
FeHepat	8.22E-13	-3.76E-12	1.058060	-7.05E-13	-1.056880	0.253629	-0.299648	1.41E-12	-1.53E-12
Tf	-0.061360	1.36E-12	6.82E-13	3.41E-13	0.363034	0.256105	-0.257580	0.0613475	5.12E-13
Hepcidin	0	0	0	0	0	0	0	0	0
FeTf	-0.284521	-5.14E-12	-2.57E-12	-5.93E-13	-1.411820	-0.996059	1.003780	0.284463	-1.98E-12
FeTf1	0.518123	-1.08E-12	-5.40E-13	-9.00E-13	-0.247240	-0.174347	0.173546	-0.518018	-3.60E-13
NTBI	-0.802228	0.003428	0.116328	-3.59E-13	-0.893291	-0.821855	0.828849	-0.196905	-1.26E-12
FeRest	4.70E-13	-3.60E-12	-2.03E-12	-4.70E-13	-7.83E-13	-3.13E-12	4.89E-14	1.72E-12	-1.57E-12
FeBM	7.04E-13	-3.80E-12	-1.83E-12	-0.999001	-0.999001	-0.704779	0.709476	1.83E-12	-1.41E-12

	VhepatNTBI	VmacroNTBI	VrestNTBI	vRBCMacro	krestOUT	kInBM	Diet	Hepcidin Synthesis	Hepcidin Decay
FeGut	0	0	0.037045	0	-0.036632	0	1.236130	1.194040	-1.192300
FeRBC	1.25E-12	-2.68E-12	0.712719	-0.999001	-0.704779	1	0.992750	-0.708802	0.709504
FeMacro	1.96E-12	-1.148330	0.819468	-1.18E-12	-0.810167	1.149830	1.141490	0.328799	-0.328442
FeHepat	-1.056880	-2.70E-12	0.754088	-9.39E-13	-0.745625	-1.53E-12	1.050390	0.302578	-0.302265
Tf	-3.41E-13	8.53E-13	-0.258947	3.41E-13	0.256105	5.12E-13	-0.360676	0.257567	-0.257779
Hepcidin	0	0	0	0	0	0	0	1	-0.999001
FeTf	1.78E-12	-3.36E-12	1.007490	-7.91E-13	-0.996059	-1.78E-12	1.403390	-1.001740	1.002940
FeTf1	-1.80E-13	-5.40E-13	0.175939	-7.20E-13	-0.174347	-5.40E-13	0.244963	-0.175343	0.175146
NTBI	1.79E-12	-2.51E-12	0.831401	-5.38E-13	-0.821855	0.608349	1.158140	-0.826545	0.827650
FeRest	1.25E-12	-2.35E-12	-4.07E-12	-9.39E-13	-0.999001	-1.57E-12	1	-3.13E-13	-2.82E-12
FeBM	1.55E-12	-2.54E-12	0.712719	-7.04E-13	-0.704779	1	0.992750	-0.708802	0.709504

Methodology



Features

- Modeled rates of injected radioactive iron transport between organ compartments
- Mice of 3 different diets in experimental data
- SBML File Available

- Mass Action Rate Laws
- NTBI and FeTf in Plasma
- Fewer Compartments

Contains:
- Transferrin
- Hepcidin Synthesis & Degradation
- Inhibition of iron export by Hepcidin

- Tracks normal and radioactive iron separately
- Contains Steady States
- Has predictive power

Model Equations

The rate laws used in the model are listed in the table to the right. In COPASI, a rate law is the symbolic form of one term of the differential equations

v = *rate of reaction*

S = *substrate*

S^* = *competitive inhibitor*

$\forall$ = *volume of substrate's compartment*

M = *modifier* $(FeTf)$

$C, k, h, K_m, K_i, M_{halve}$ = *constants*

Rate Law Name	Equation	Reactions
Constant Flux	$v = C$	Diet Hepcidin Synthesis (constant hepcidin model)
Mass action (Same compartment)	$v = k * S$	NTBI->FeTF1 FeTf1->FeTf Rest->Out Hepcidin Decay
Mass action (Different compartments)	$v = k * \forall * S$	FeTf->BM FeTf->Hepat FeTf->Rest FeTf->Gut FeTf1->BM FeTf1->Hepat FeTf1->Rest FeTf1->Gut RBC->Macro
Henri-Michaelis-Menten	$v = \frac{v_{max} * S}{K_m + S}$	
Noncompetitive Inhibition	$v = \frac{v_{max} * \forall * S}{(K_m + S)(1 + \frac{I}{K_i})}$	
Mixed Competitive / Noncompetitive Inhibition	$v = \frac{v_{max} * \forall * S}{(K_m + S + S^*)(1 + \frac{I}{K_i})}$	Gut->NTBI Macro->NTBI Hepat->NTBI Rest->NTBI
Hill	$v = \frac{V * M^h}{{M_{halve}}^h + M^h}$	Hepcidin Synthesis (variable hepcidin model)

References

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