Mathematical Modeling of Intestinal iron absorption using Genetic Programming

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> Conclusions

- Iron absorption fluxes in Caco-2 cells were determined experimentally.
- A mathematical model was developed that allows predicting the amount of iron entering the cell at a given time, considering different initial iron concentrations in the intestinal lumen (apical side).
- The model was developed using a nonlinear regression with a genetic programming method, adding an additional parameter optimization stage.
- The model obtained can accurately represent the experimental data and captures the main characteristics of the biological phenomenology of the system.

> Introduction

Iron is a trace metal essential for most living organisms. Iron levels present in a cell must be highly controlled since increased or decreased iron concentrations can trigger numerous diseases such as hemochromatosis and anemia.

In humans, control of iron levels in the organism lies on the regulation of intestinal absorption, as there is no specialized mechanism for its excretion. The absorption process can be divided in three stages: first, iron enters to cells as a ferrous ion from the intestinal lumen through the transporter protein DMT1 located on the apical (lumen) side of the cell. Then the metal is transported within the cell, and finally it is transported outside the cell on the basolateral (blood stream) side through the protein FPN1 (Fig.1).

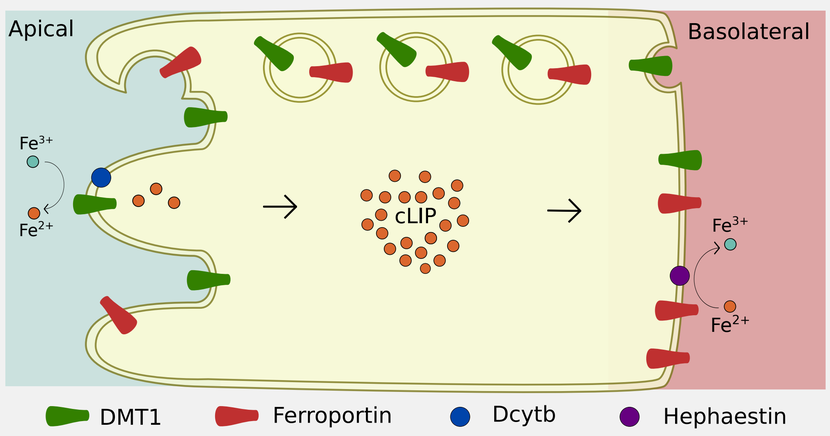

Figure 1: Main components of intestinal non-heme iron absorption.

Due to the high relevance and complexity of the iron absorption process, **a mathematical model is required that can help describe the amount of iron that enters an organism under different conditions**. Unfortunately, little information is available regarding the components involved in the phenomenon and their interactions. Hence, a methodology that allows creating a model based on experimental data, without knowing the system in full detail is required. The objective of this work is to obtain a mathematical model that allows representing iron absorption fluxes in time, for different initial iron concentrations on the apical media, using genetic programming.

> Methods

***In vitro* procedure**

The amount of iron entering the cell and passing through to the basolateral media on the first 15 minutes after iron exposure on the apical media was determined (training data set). DMT1 protein levels were assessed from the initial iron transport rates for different apical iron concentrations (validation data set) (Fig. 2).

***In silico* procedure**

Models for iron flux were built using a symbolic non-linear regression process using a genetic programming algorithm. Parameters and main criteria for algorithm training are described in Table 1. A parameter fitting stage for every tree was added before evaluating the fitness function. The obtained models were validated in two ways: measuring their ability to capture the validation data set and through the Jackknife cross-validation (leave-one-out) method.

Table 1: Parameters used for GP training.

Parameters	Value or criteria
Population size	500
Number of generations	100
Recombination probability	0.9
Mutation probability	0.1
Elitism	keep the best
Function set	$cos(), sin(), +, -, \times, /, a^b, ln(), exp()$
Terminal set	Var: C_0, t; Const: $1, 5, 10, 100, 1000$
Initial population	Full, Grow, Ramped-Half-and-Half
Tree depth limit	17
Selection methods	Roulette, tournament
Fitness Function	Mean Square Error (MSE)

$$MSE_{jk} = \sum_{i=1}^{N} abs(\hat{Y}_i^{(-i)} - Y_i) \quad (1)$$

$$\beta^* = \frac{1}{N}\sum_{i=1}^{N}(N\beta - (N-1)\beta_i) \quad (2)$$

$$CI(\beta^*) = \beta^* \pm t_{\alpha,\nu}\hat{\sigma}_{\beta^*} \quad (3)$$

$$r^* = Z^{-1}\left(\frac{1}{N}\sum_{i=1}^{N}(Nr - (N-1)Z(r_i))\right) \quad (4)$$

> Results

Empirical model obtained by GP algorithm

$$f(C_0, t) = sin(\beta_1 C_0) + sin(\beta_2 C_0) + sin(\beta_3 + t^{(sin(\beta_4 C_0))}) + t^{(sin(\beta_5 C_0))} \quad (5)$$

Model simulation

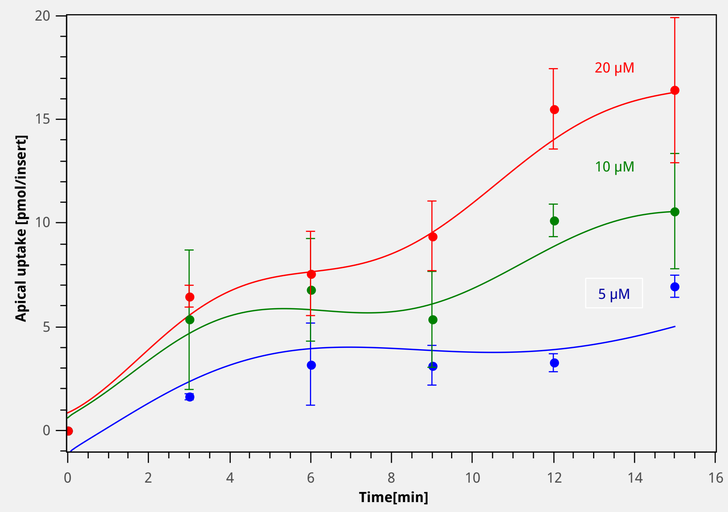

Figure 2: Iron uptake experimental data and best model simulation. Circles correspond to the average value, error bars indicate standard deviation for each sample and the curve plotted correspond to simulation results for the model described by Eq. 5 ($R^2 = 0.86$)

> Validation

Simulation of validation data set

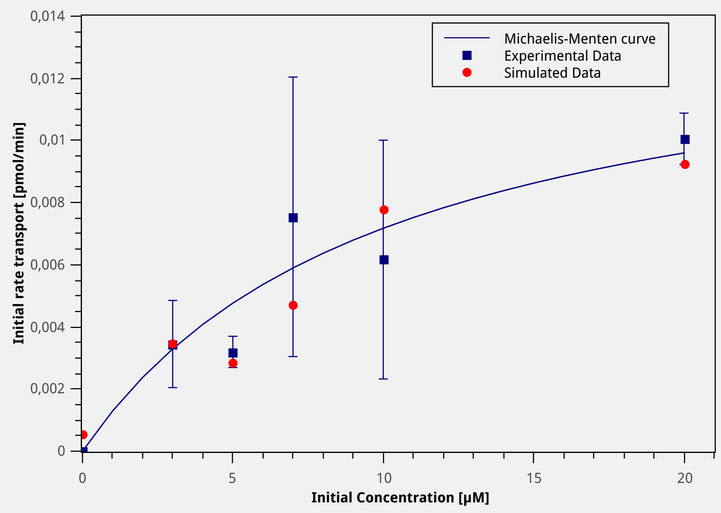

Figure 3: Initial rates of absorption experimental data and model prediction. Blue circles correspond to the average value, error bars indicate standard deviation for each sample and red circles correspond to simulation results for the model ($R^2 = 0.89$)

Jackknife validation

Table 2: Main results of Jackknife validation

Parameter	Value	Pseudo-Parameters	Confidence Intervals
β_1	4.47	4.47	$\pm 3.69 \times 10^{-2}$
β_2	6.39	6.40	$\pm 2.48 \times 10^{-2}$
β_3	4.54	2.53	$\pm 4.27 \times 10^{-1}$
β_4	6.38	6.42	$\pm 4.80 \times 10^{-3}$
β_5	6.37	6.37	$\pm 6.57 \times 10^{-3}$
Coefficient of correlation		**Population correlation (r^*)**	MSE_{jk}
0.929		0.896	1.61

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