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Uptake of fatty acids by the enterocyte: New insights gained from mathematical modeling

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Uptake of fatty acids by enterocytes is debated in the literature and usually reviewed as a dual mechanism

Passive diffusion?

CD36?

FABPpm?

Active transport?

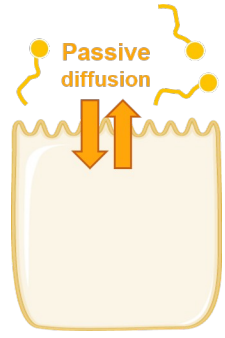
Saturable mechanism?

No membrane protein required?

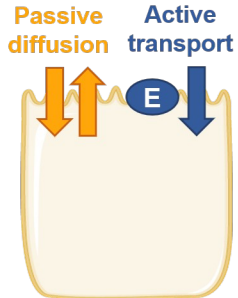
Caveolin-1?

Are the observed dose-response curves of apical enterocyte FA uptake compatible with the pathways suggested by the literature?

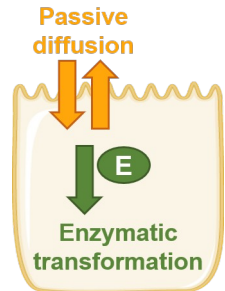
Mathematical modeling and data fitting



$$(M0) \begin{cases} \frac{d[FA_{ext}]}{dt} = -\frac{PS}{V_{ext}} ([FA_{ext}] - [FA_{in}]) \\ \frac{d[FA_{in}]}{dt} = \frac{PS}{V_{in}} ([FA_{ext}] - [FA_{in}]) \end{cases}$$

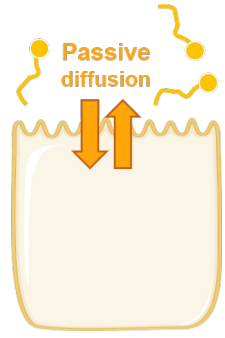


$$(M1) \begin{cases} \frac{d[FA_{ext}]}{dt} = -\frac{PS}{V_{ext}} ([FA_{ext}] - [FA_{in}]) - \frac{k_{cat}[E][FA_{ext}]}{K_M + [FA_{ext}]} \\ \frac{d[FA_{in}]}{dt} = \frac{PS}{V_{in}} ([FA_{ext}] - [FA_{in}]) + \frac{k_{cat}[E][FA_{ext}]}{K_M + [FA_{ext}]} \frac{V_{ext}}{V_{in}} \end{cases}$$

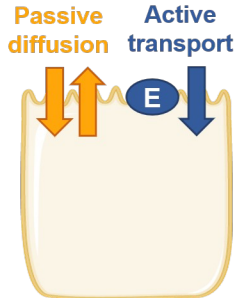


$$(M2) \begin{cases} \frac{d[FA_{ext}]}{dt} = -\frac{PS}{V_{ext}} ([FA_{ext}] - [FA_{in}]) \\ \frac{d[FA_{in}]}{dt} = \frac{PS}{V_{in}} ([FA_{ext}] - [FA_{in}]) - \frac{k_{cat}[E][FA_{in}]}{K_M + [FA_{in}]} \\ \frac{d[FA_{transformed}]}{dt} = \frac{k_{cat}[E][FA_{in}]}{K_M + [FA_{in}]} \end{cases}$$

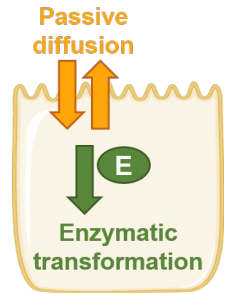
Uptake parameter	Value
P	14.8 dm/min
$\frac{V_{ext}}{V_{in}}$	min=1 ; max=1000



$$(M0) \begin{cases} \frac{d[FA_{ext}]}{dt} = -\frac{PS}{V_{ext}} ([FA_{ext}] - [FA_{in}]) \\ \frac{d[FA_{in}]}{dt} = \frac{PS}{V_{in}} ([FA_{ext}] - [FA_{in}]) \end{cases}$$



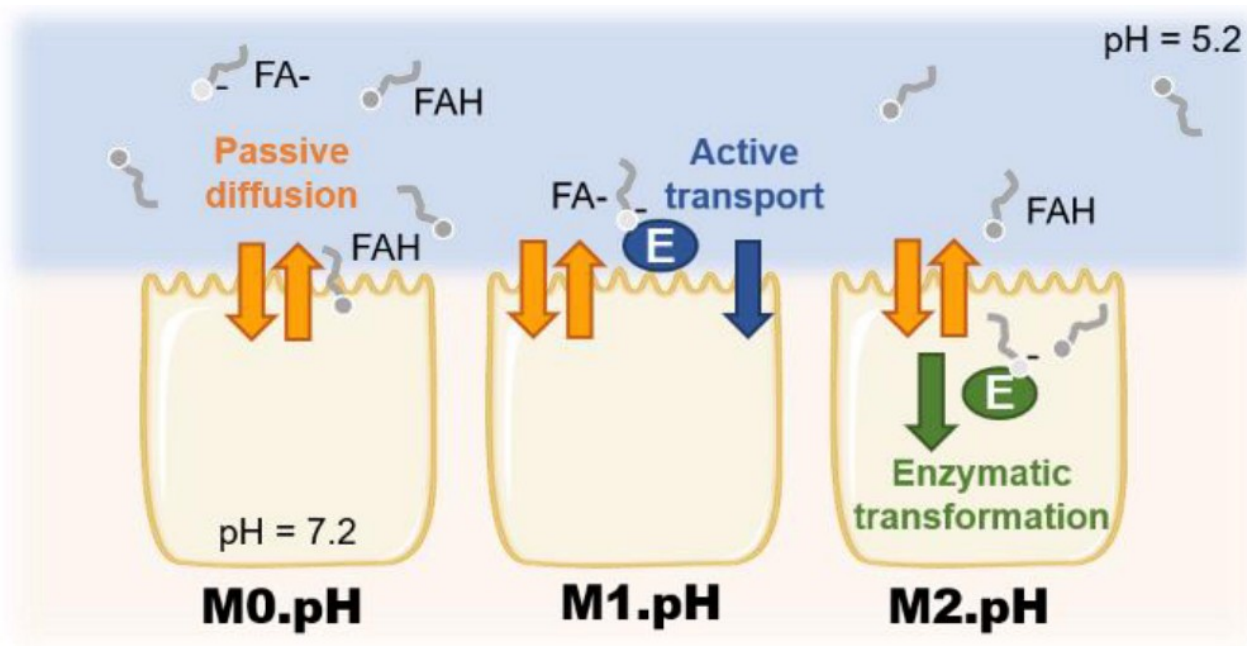
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$$(M2) \begin{cases} \frac{d[FA_{ext}]}{dt} = -\frac{PS}{V_{ext}} ([FA_{ext}] - [FA_{in}]) \\ \frac{d[FA_{in}]}{dt} = \frac{PS}{V_{in}} ([FA_{ext}] - [FA_{in}]) - \frac{k_{cat}[E][FA_{in}]}{K_M + [FA_{in}]} \\ \frac{d[FA_{transformed}]}{dt} = \frac{k_{cat}[E][FA_{in}]}{K_M + [FA_{in}]} \end{cases}$$

Uptake parameter	Value
P	14.8 dm/min
$\frac{V_{ext}}{V_{in}}$	min=1 ; max=1000
k_{cat}	min=10 ^{0.78} ; max=10 ^{4.78} min ⁻¹
$\frac{k_{cat}}{K_M}$	min=10 ^{-1.22} ; max=10 ^{2.78}

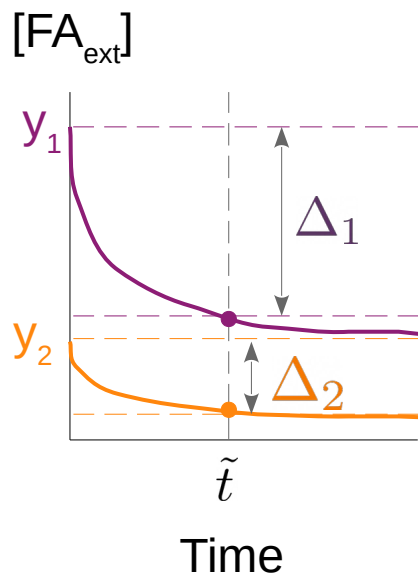
pH variation of each model:



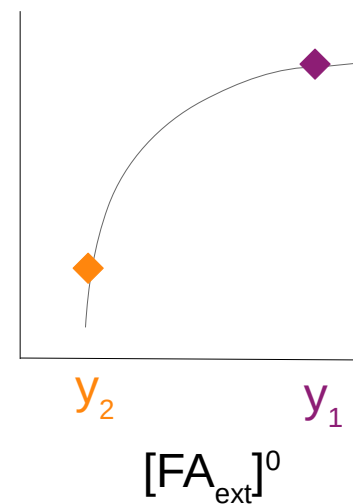
pKa = 7.5

Obtaining dose-response curves from our models:

\tilde{t} : collection time

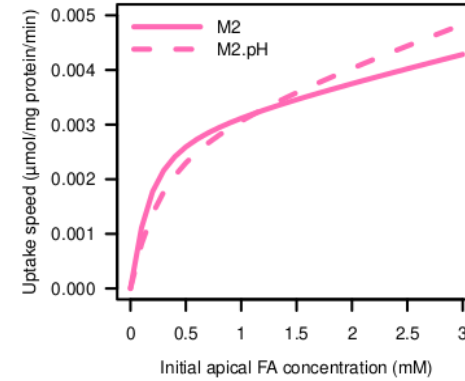
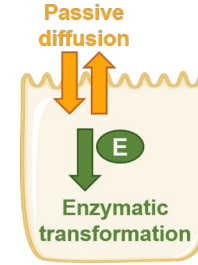
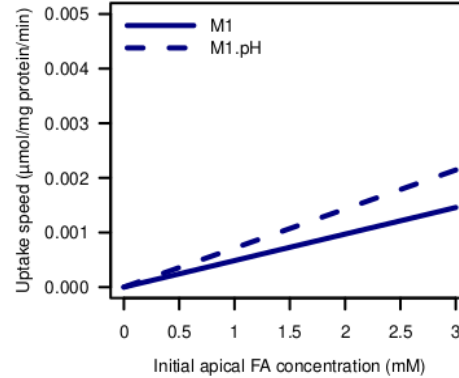
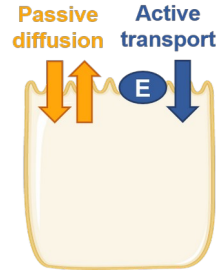
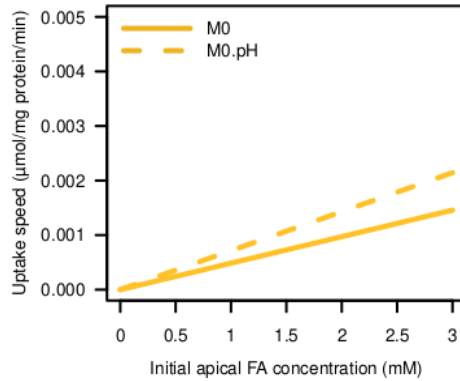
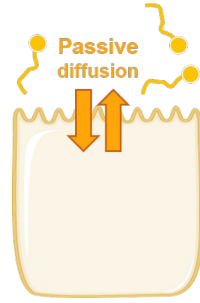


Uptake



Result 1

Dose-responses

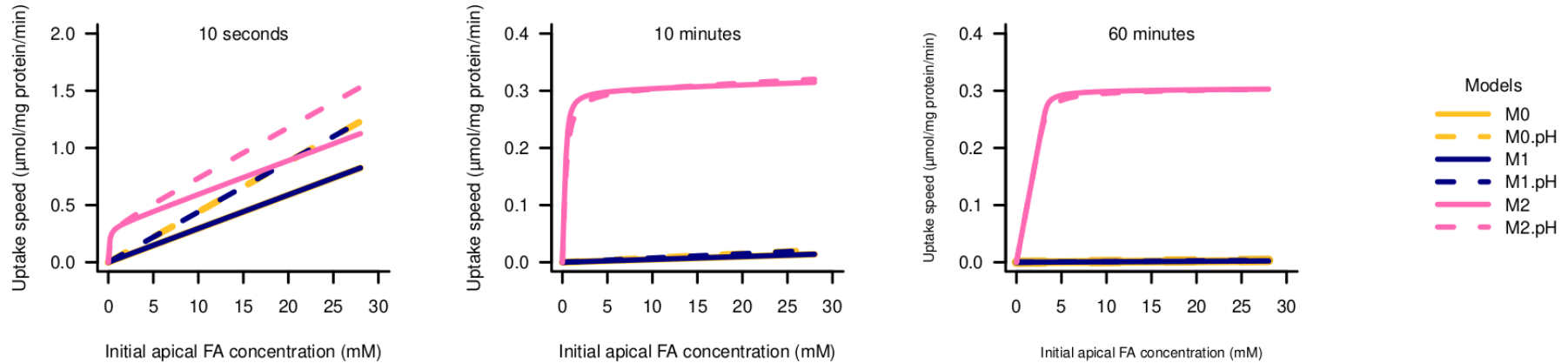


pH increases the uptake response

For intermediate parameter values
Dose-responses : collection time set to 10min

Further study of dose-responses at different collection times

For parameter maximizing the uptake



M2 and M2.pH enable greater uptake responses and slope discontinuities

Experimental data

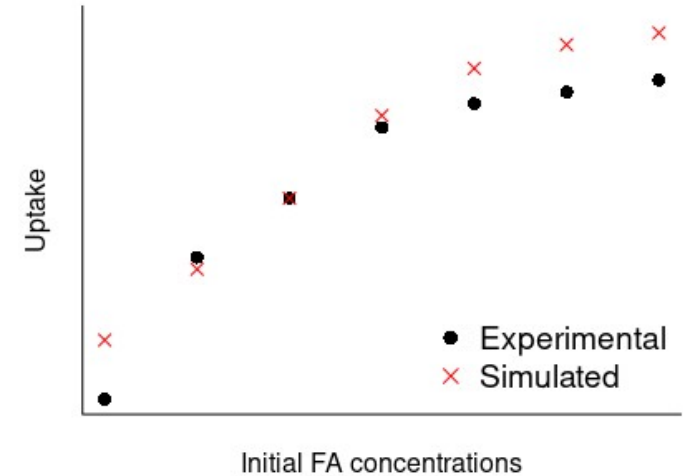
- 7 datasets
- Digitized from research papers using WebPlotDigitizer¹
- Expressed in the same units of measure ($\mu\text{mol}/\text{mg}$ protein/ min) using conversion factors found in the literature

¹ Rohatgi, A. (2020). WebPlotDigitizer (Pacifica, California, USA)
<https://automeris.io/WebPlotDigitizer/>

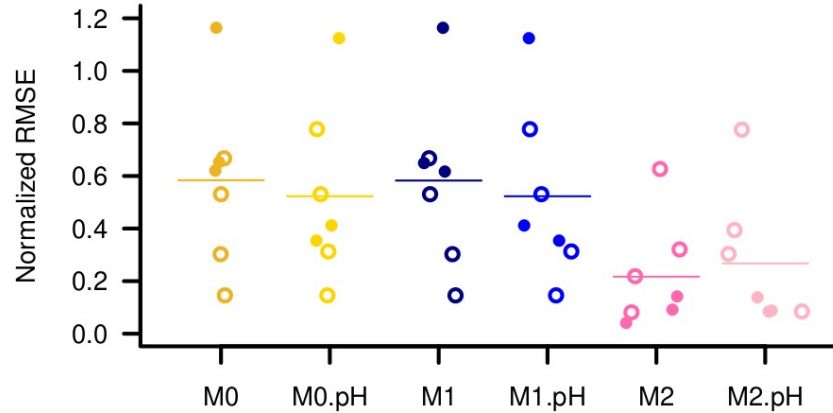
$$k_{cat} \quad \frac{k_{cat}}{K_M} \quad \frac{V_{ext}}{V_{in}}$$

Data fitting

- MCMC algorithm (FME package, R) (Bayesian methods)
- Parameter *a posteriori* distributions
 - We have >1,000 values for each parameter for each model and each dataset



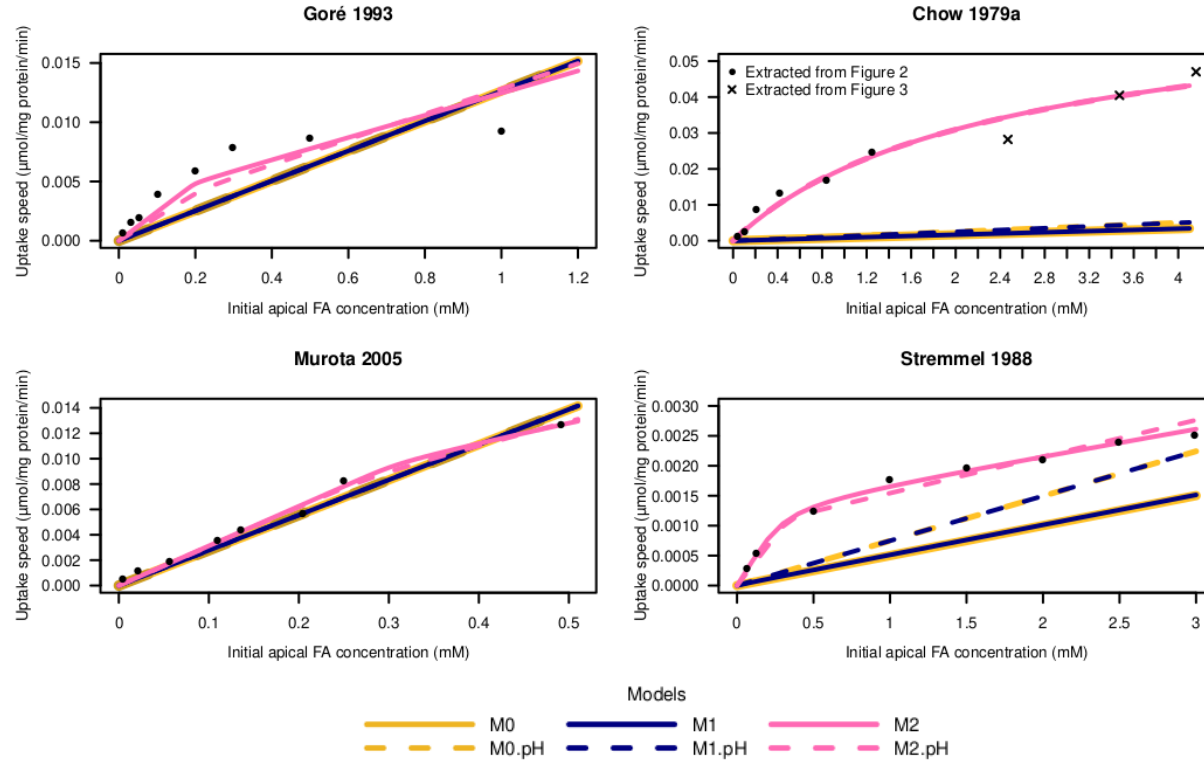
Quality of fits



M2 and M2.pH show better quality of fits
(The lower the normalized RMSE, the better the fit)

Result 4

Data fitting



- Responses of M0 and M1 are far from data (even with pH)
- Responses of M2 and M2.pH are close to data

Only M2 and M2.pH show slope discontinuities

Chow, S.L., and Hollander, D. (1979a) J. Lipid Res. 20, 349–356.
Goré, J., and Hoinard, C. (1993) J. Nutr. 123, 66–73.
Murota, K., and Storch, J. (2005). J. Nutr. 135, 1626–1630.
Stremmel, W. (1988). J. Clin. Invest. 82, 2001–2010.

Take-home messages

- pH enhances uptake
- Passive diffusion alone (M0) is not sufficient to provide realistic uptake responses
- Adding an intracellular enzymatic transformation of FA (M2) is more efficient for the enterocyte than adding a membrane protein (M1)


Perspectives

- New experimental uptake data to improve our understanding
- Gaining insights on sensitive topics using quantitative and mechanistic modeling



Open to discussion!

Images: <https://www.pindipati.com/>

On-going submission of a research paper 

Thank you to the GERLI committee

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