The Transit Compartment Model:
The Truth Behind n!

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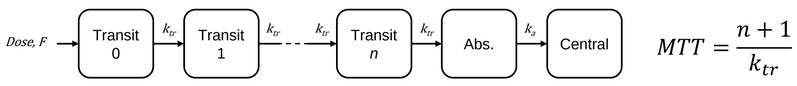
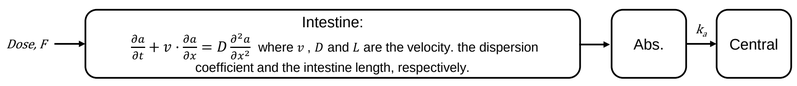
Background

- The transit compartment (TC) model was first introduced by Yu *et al.* [1], and popularized by Savic *et al.* [2] to better describe drug absorption delay as a compromise between simpler model (*e.g.* lag-time model) and more complex model (*e.g.* physiological-based absorption pharmacokinetics models).
- Yu *et al.* compared the TC model to the dispersion model, which is considered more physiological, but difficult to implement, while having the same number of parameters. They also concluded that both models describe data equivalently.
- The equivalence shown by Yu *et al.* is not a coincidence, as there is a mathematical explanation which will be demonstrated.



$$MTT = \frac{n+1}{k_{tr}}$$

VS



Methods

- Analytical solution with $Dose = F = 1$:
  - TC Model:

$$a_{\mathrm{i,TC}}(\mathrm{t}) = \frac{(k_{tr} \cdot t)^i}{i!} \cdot \mathrm{e}^{-k_{tr} \cdot t} \quad \forall i \in [\![0 : n]\!] \tag{1}$$

  - Dispersion Model:

$$a_D(\mathrm{x}, \mathrm{t}) = \frac{\mathrm{e}^{-\frac{(x - v \cdot t)^2}{4Dt}}}{\sqrt{4\pi D t}} \quad \forall x \in [0 : L] \,\&\, \forall t \geq 0 \tag{2}$$

- To link both models, the first order upwind scheme [3] was applied to the advection equation (*i.e.* the dispersion equation when $D = 0$) which gives:

$$\frac{\partial a_i}{\partial t} \approx \frac{v}{dx} \cdot (a_{i-1} - a_i) \quad \forall i \in [\![0 : n]\!] \tag{3}$$

- This scheme is known to introduced numerical diffusion, which can be shown by the 2nd order Taylor expansion [3]:

$$\begin{aligned} \frac{\partial a_i}{\partial t} &\approx \frac{v}{dx} \cdot (a_{i-1} - a_i) \\ &\approx -v \cdot \frac{\partial a_i}{\partial x} + \frac{v dx}{2} \cdot \frac{\partial^2 a_i}{\partial x^2} + o(dx^2) \end{aligned} \quad \forall i \in [\![0 : n]\!] \tag{4}$$

- Finally, the output rate of both models are compared when:

$$v = dx \cdot k_{tr} = \frac{n+1}{n \cdot MTT} \quad \text{and} \quad D = \frac{v \cdot dx}{2} = \frac{n+1}{2 \cdot n^2 \cdot MTT}$$

with $dx = \frac{L}{n}$ and $L = 1$ (Note: The value of L is not relevant as all constants can be normalized).

Results

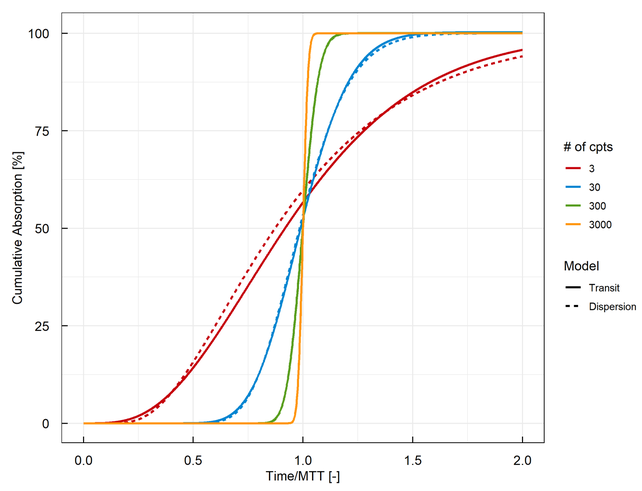


Figure 1: Comparing the cumulative absorption of the TC and dispersion models over time for various number of compartments.

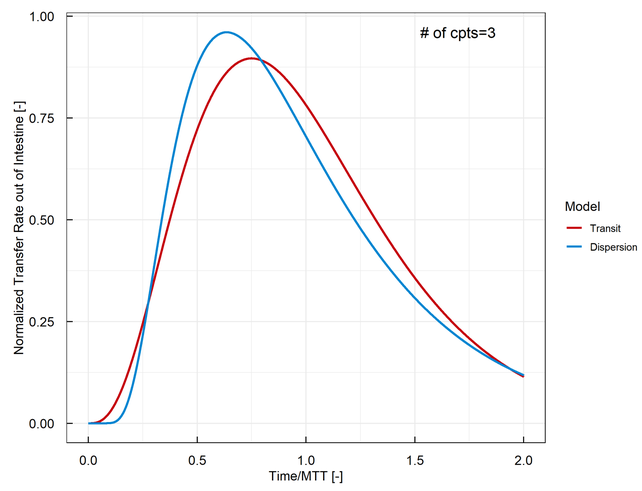


Figure 2: Comparing the normalized transfer rate out of intestine of the TC and dispersion models over time when the number of compartments is 3.

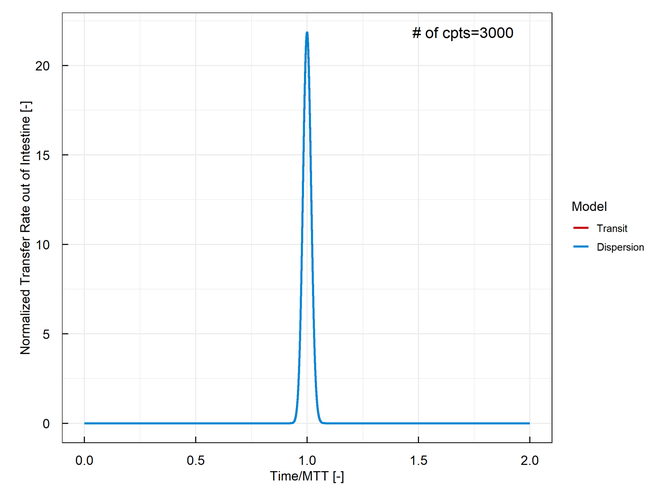


Figure 2: Comparing the normalized transfer rate out of intestine of the TC and dispersion models over time when the number of compartments is 3000.

Conclusion

- When estimating n and MTT within the TC model, it is equivalent to estimate v and D with the dispersion model, which mathematically confirms Yu *et al.* conclusion.
- TC Model:
  - Advantages:
    - Very intuitive structure.
    - When the ODE version is used, the computation time is faster as the number of compartments n is smaller for the TC model than for the dispersion model (where n is chosen to minimize error).
  - Disadvantages:
    - The mechanism of dispersion is hidden.
    - When the ODE version is used, multiple models need to be tested as different n are tested.
- Dispersion Model:
  - Advantages:
    - The mechanism of dispersion is explicitly expressed.
    - The schematic representation of PDEs is more elegant than the TC model representation.
    - When discretized, n is fixed to minimize numerical error while v and D are estimated, therefore no need to test multiple models as with the TC model.
  - Disadvantages:
    - Complexity in selecting the right discretization scheme, which is problem dependent.
    - There is a risk that the required n leads to a high number of ODEs, and consequently increases computation time.
- Take home message:
  - We, pharmacometricians, would benefits in learning more about PDEs to better manipulate the mathematical objects that we use.
  - The TC model is simply a dispersion model in disguise.

References

[1] L.X. Yu, J.R. Crison, G.L. Amidon, *Compartmental transit and dispersion model analysis of small intestinal transit flow in humans*, International Journal of Pharmaceutics, 140 (1), 111–118, 1996, https://doi.org/10.1016/0378-5173(96)04592-9.
[2] R.M. Savic, D.M. Jonker, T. Kerbusch *et al.*, *Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies*, Journal of Pharmacokinetics and Pharmacodynamics, 34, 711–726, 2007, https://doi.org/10.1007/s10928-007-9066-0.
[3] C. Hirsch, *Numerical Computation of Internal and External Flows*, John Wiley & Sons,, Second Edition, 2007, ISBN: 978-0-7506-6594-0.