# Lua Interface for Customising ADAM Model Functions

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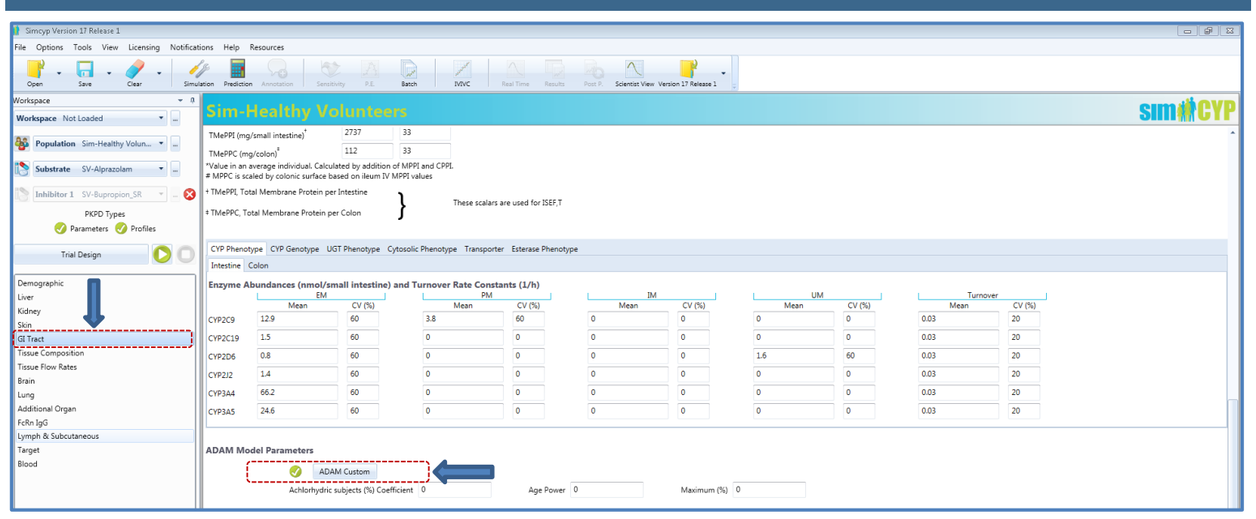
## Introduction

- Advanced application of commercial PBPK software can be restricted because users do not have access to the source code.
- Thus, the built-in models or individualised physiological parameters cannot be modified albeit that alternative models can be selected via screen options .
- For example, the gastric emptying function within absorption PBPK modelling framework is usually modelled as a first order process.
- However, gastric emptying of solids and liquids can have biphasic or more complex patterns; e.g., for solids there may be a lag phase during which little emptying occurs, followed by a linear (zero order) emptying phase, that is independent of gastric volume[1].
- Simcyp version 17.1 however now provides an interface facility for users to customise in-built ADAM models and parameters.

## Customised ADAM Functions



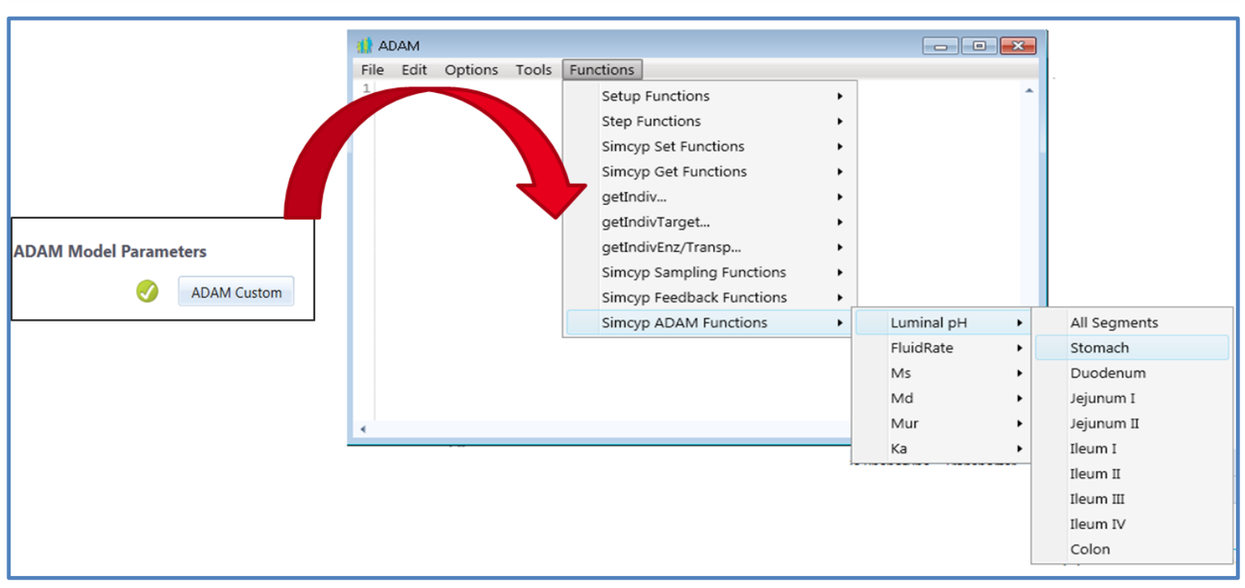




**Fig. 1.** Structure and location of custom ADAM Model functions in Simcyp® V17. Population>>GI Tract>>ADAM Custom>>Simcyp ADAM Functions.

- The interface language used for customising ADAM functions is Lua. Lua together with its interpreter/compiler is very lightweight and flexible, so can easily be embedded in other programs[2].

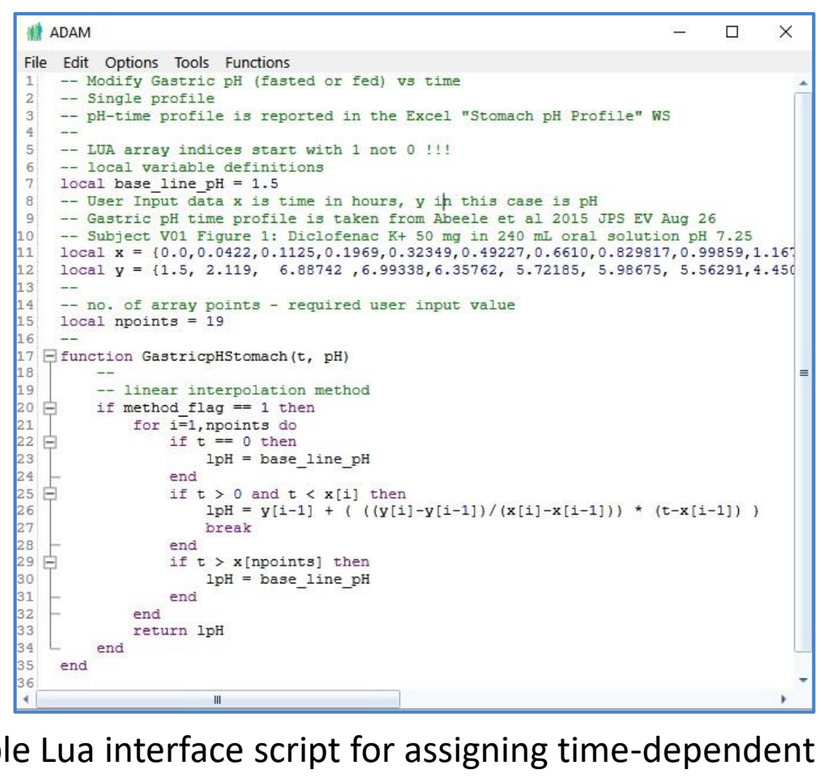



**Fig. 2.** Sample Lua interface script for assigning time-dependent gastric pH via interpolation of measured values.

## Applications

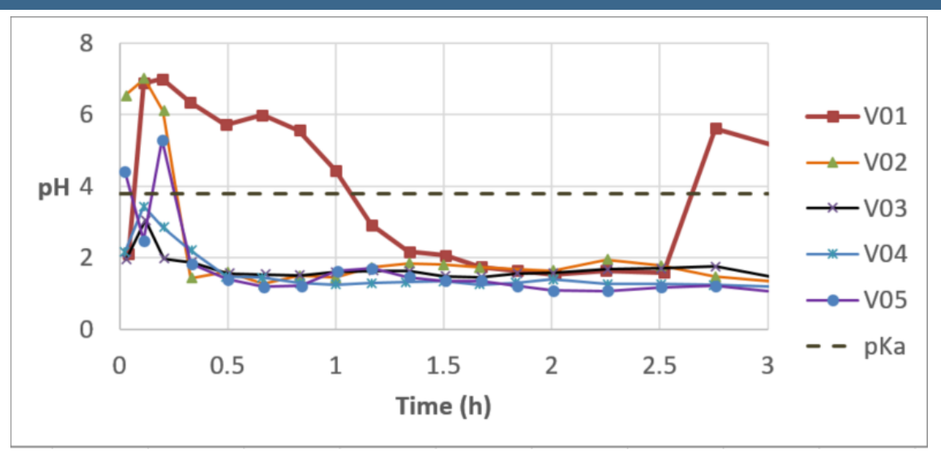



**Fig. 3.** Individual fasted pH in gastric aspirates vs. time in the presence of dissolved diclofenac sodium (van den Abeele et al. 2015).

- Recently, van den Abeele et al. explored gastrointestinal dissolution, supersaturation and precipitation of the acidic drug diclofenac in humans[3].
- A 50 mg potassium diclofenac tablet was administered and gastric fluids were aspirated at intervals & dissolved and total diclofenac and pH (Fig. 3) measured.
- The current default luminal fasted pH function within the simulator is static - pH cannot change as a function of time (Fig. 4).

| | General | Water Physicochemical Properties | Luminal pH | Luminal Bicarbonate | Luminal Fluid Velocity | Luminal Bile Salts | GI Morphology | Luminal Boundar |
|---|---|---|---|---|---|---|---|---|
| | Stomach | Duodenum | Jejunum I | Jejunum II | Ileum I | Ileum II | Ileum III | Ileum IV | Colon |
| pH Fasted | 1.5 | 6.4 | 6.5 | 6.6 | 6.8 | 7 | 7.1 | 7.3 | 6.5 |
| CV pH Fasted (%) | 38 | 16 | 13 | 11 | 10 | 10 | 7 | 6 | 15 |

**Fig 4.** Default Static pH model within Simcyp.

- Diclofenac is a low pKa (3.8) acid and its solubility is sensitive to the range of pH indicated in Fig. 3 which ranges from 2 units above and below the pKa. Thus, it is useful to be able to assess the likely impact on simulation outcomes of dynamic rather than static pH.
- ADAM Lua interface can be used to intervene in the current static pH model and dynamic time-dependent pH profiles can be simulated in V17.1 (Fig. 2).
- Although the availability of luminal pH data is rare, the Lua interface can be used to study the impact of acid regulating agents (ARAs) on co-administered drugs; gastric pH profiles of commonly used ARAs at therapeutic doses have been reported[4,5,6].
- Lua interface together with the PD module has been used to model pH-feedback with a PPI (see Poster Rose *et al.*).
- Currently Lua interface can be used to access or intervene in a number of ADAM model functions across all GI-compartments including: **a)** GI-Luminal pH; **b)** Fluid rate (volume) (i.e., gastric emptying); **c)** Drug mass dissolved; **d)** Drug mass undissolved; and **e)** Absorption rate constant.
- Additional simulator state variables can be accessed using codes indicated on the Excel Output WS “Ode State Info”.
- The long term plan is to provide libraries of example scripts.

## References

1. Siegel et al. Gut. 1988; 29(1): 85–89.
2. www.lua.org
3. Van den Abeele et al. J Pharm Sci. 2016;105(2):687-96.
4. Goh et al. Neurogastroenterol Motil. 2016; 22(3): 355-366.
5. Hetzel et al. Br J Clin Pharmac. 1984; 18: 587-590
6. Shimatani et al. Clin Pharmacol Ther. 2006; 79 (1): 44-52