The utility of the Artificial Stomach Duodenum system in *in vivo* oral absorption modeling

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Outline

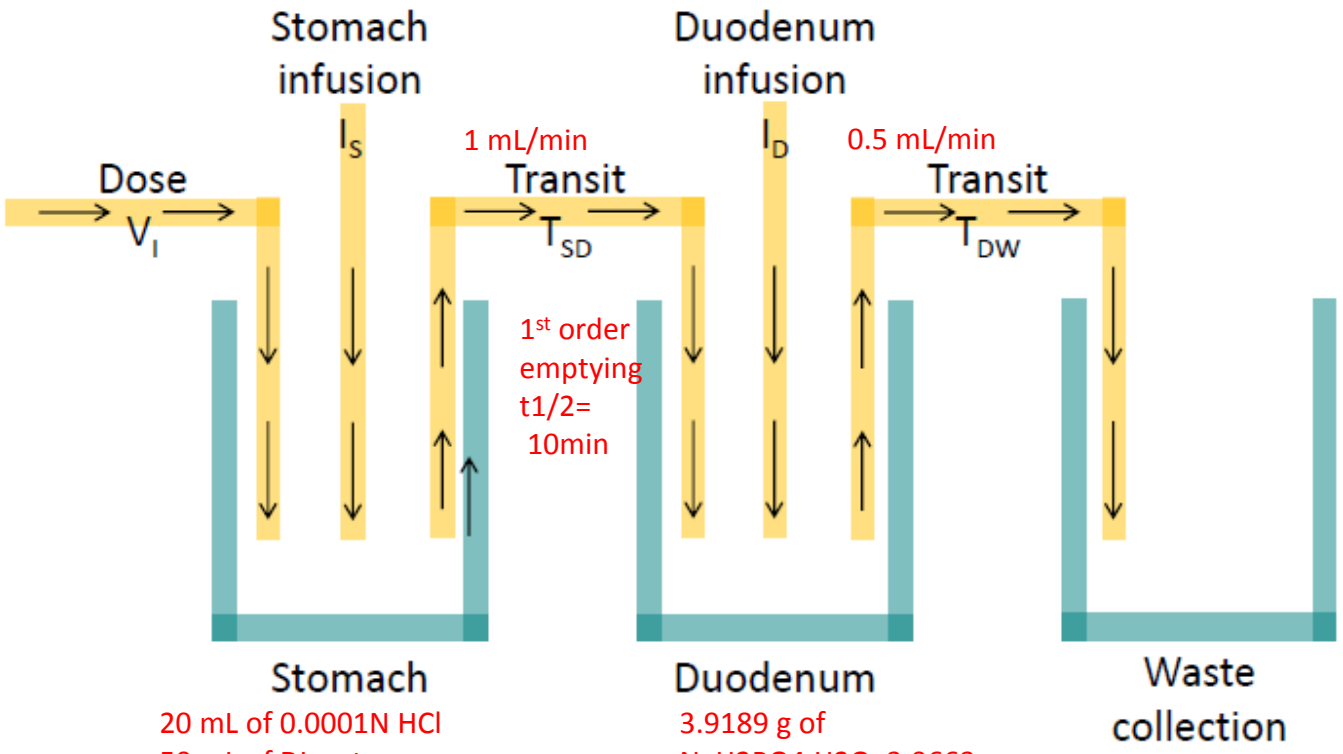
- Study objectives
- Experimental setup
- gCOAS ASD in silico model
- Simulation results
- Oral absorption simulations
- Conclusions

Study Objectives

- Understand the extent of precipitation for different salts of a Lilly molecule in the GI tract
- Extract precipitation kinetic parameters from the ASD in vitro experiments to be used in the in vivo oral absorption model

Experimental setup

All experiments were done under dog fasted conditions



Nucleation Models

- **Classical nucleation:**
  - $J_{prim} = lnA_0 \left(\frac{-16\pi(\alpha\sigma)^3 v^2{}_0}{3k^3T^3 lnS^2} \right)$
  - Parameters to be estimated: pre-exponential factor and the surface energy correction factor.
- **Power law kinetics:**
  - $J_{prim} = lnk_n \left(\frac{\Delta C}{\rho_c} \right)^n \exp(\frac{-E_{A,n}}{RT})$
  - Parameters to be estimated: nucleation coefficient, nucleation order, and the activation energy.
- **Custom kinetics:**
  - E.g., extracting nucleation rates from probability distribution functions of induction time $P(t) = 1 - \exp(jV\left(t - t_g\right))$
  - Input nucleation rate as a function of physiological parameters : J_{prim}= fcn(pH, C_{bile})

Growth model

- Surface integration limited growth:

$$\Phi_{diss} = k_g (1 - S_{rel})^{n}$$

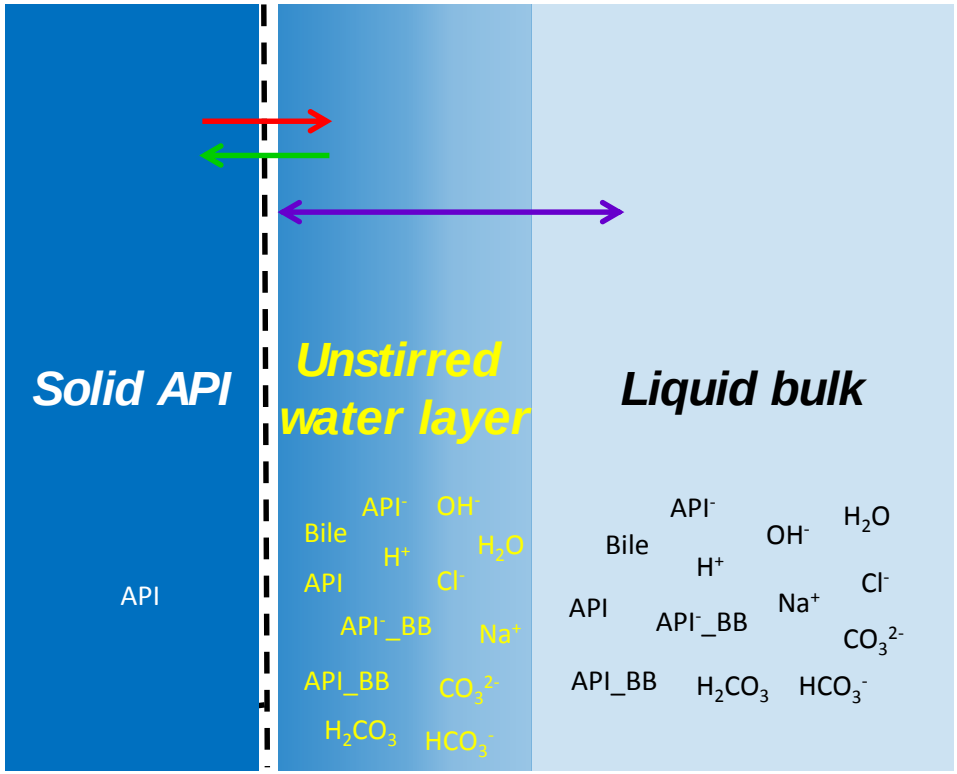
Φ_{diss}: flux of an individual specie leaving the solid due to dissolution

k_g: surface integration rate constant

S_{rel}: relative supersaturation $\frac{C}{C^{sat^{MW}}}$

n: surface integration order

Dissolution



Dissolution

Growth

Diffusion

Species in liquid phase:

API; API^-; API_BB; API^-_BB; Bile; H_2O; H^+; OH^-; H_2CO_3; HCO_3^-; CO_3^{2-}; Na^+; Cl^-

At the solid-liquid interface:0 = {dissolution} + {reaction} + {diffusion}

$$K_j = \prod_{i=1}^{NC} (C_i^s)^{\nu_{ij}},\ j = 1,..,NR$$

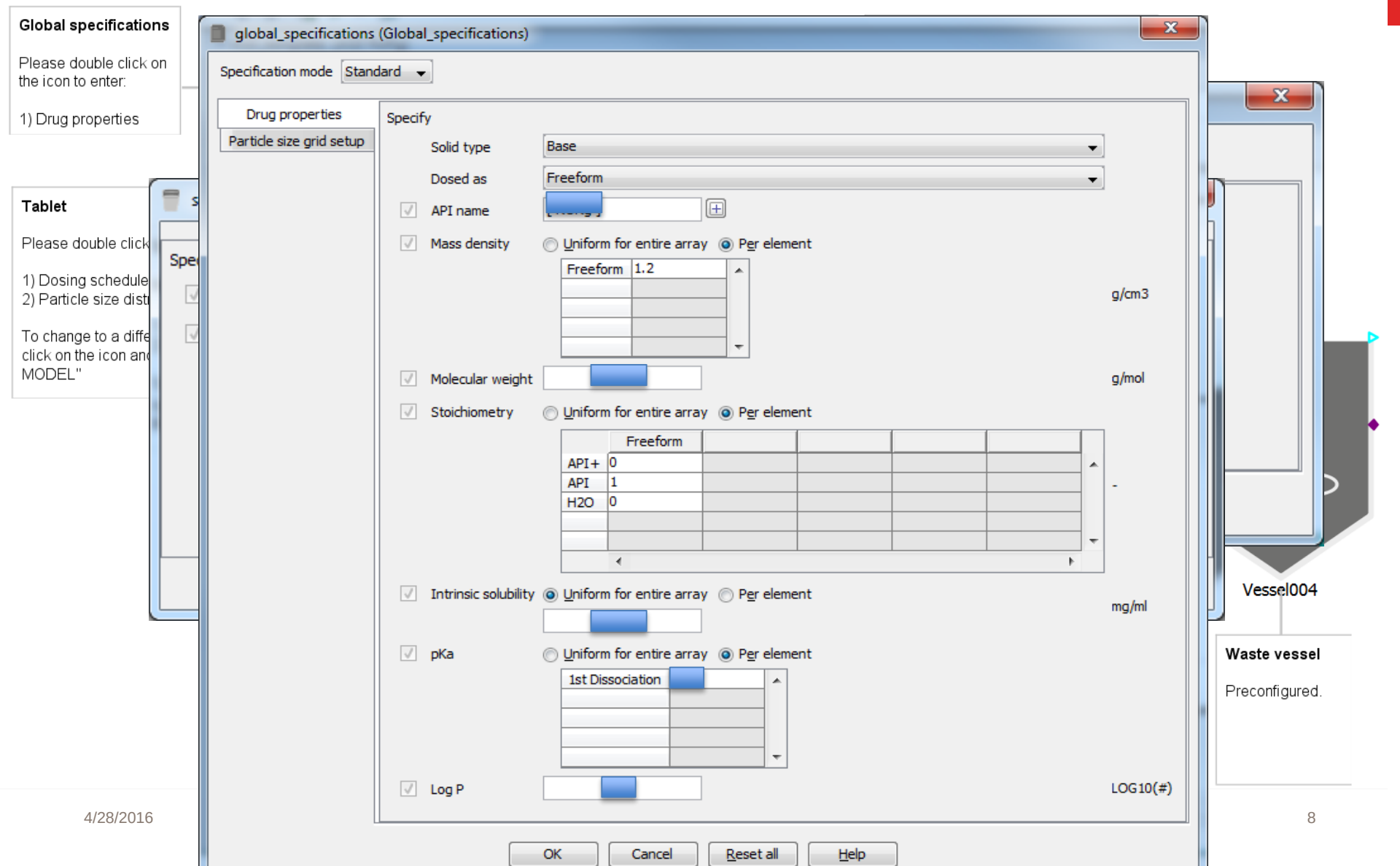
$$C_{i^*}^s = S_0$$

$$0 = R_{i^*}\delta_{i,i^*} + \sum_{j=1}^{NR} \nu_{ij} r_j - \frac{D_i}{h}\left(C_i^s - C_i^b\right), \qquad i = 1,..,NC$$

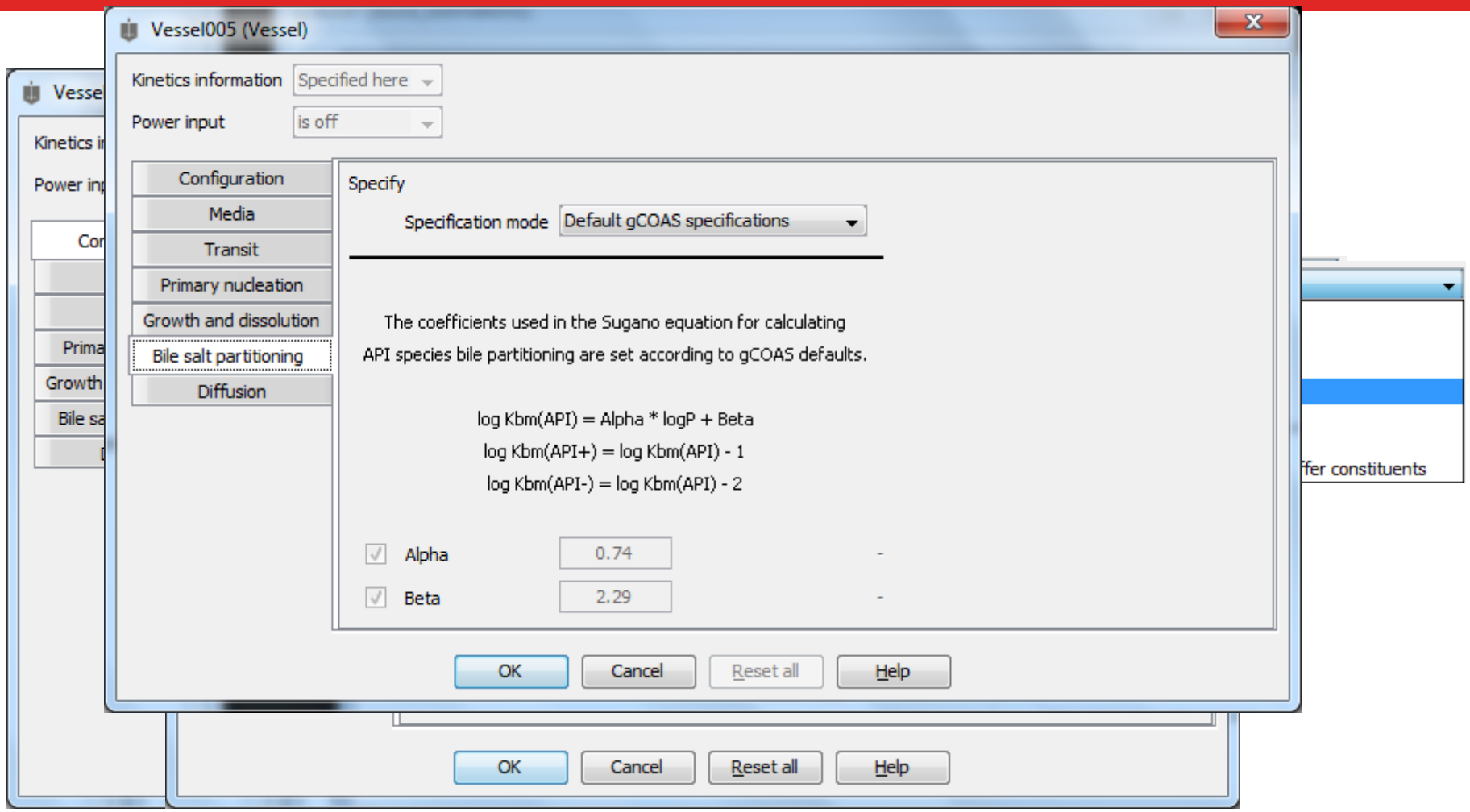
Bermingham, S. K. (2013). *Oral Absorption Modeling for Targeted Drug Product Design. The Advanced Process Modeling Forum*. London, UK.

7

gCOAS ASD in silico model

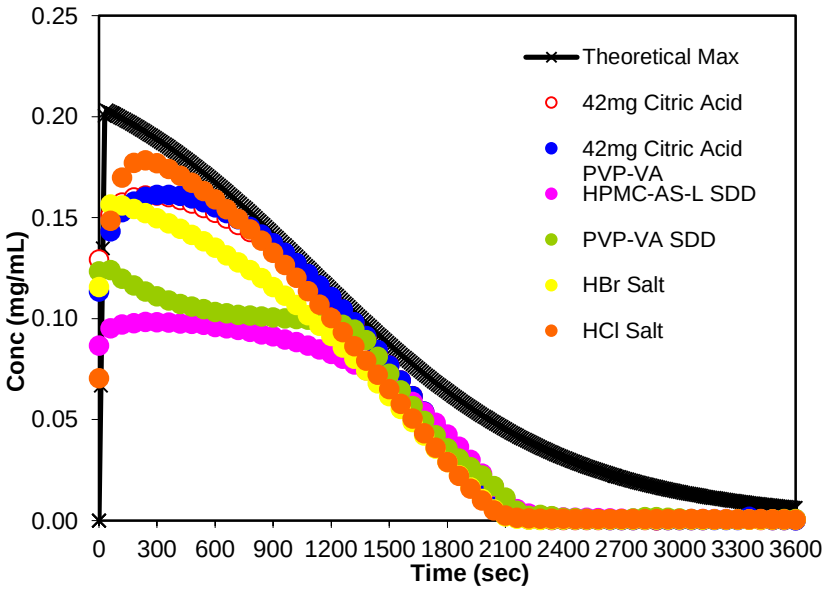


Simulation setup

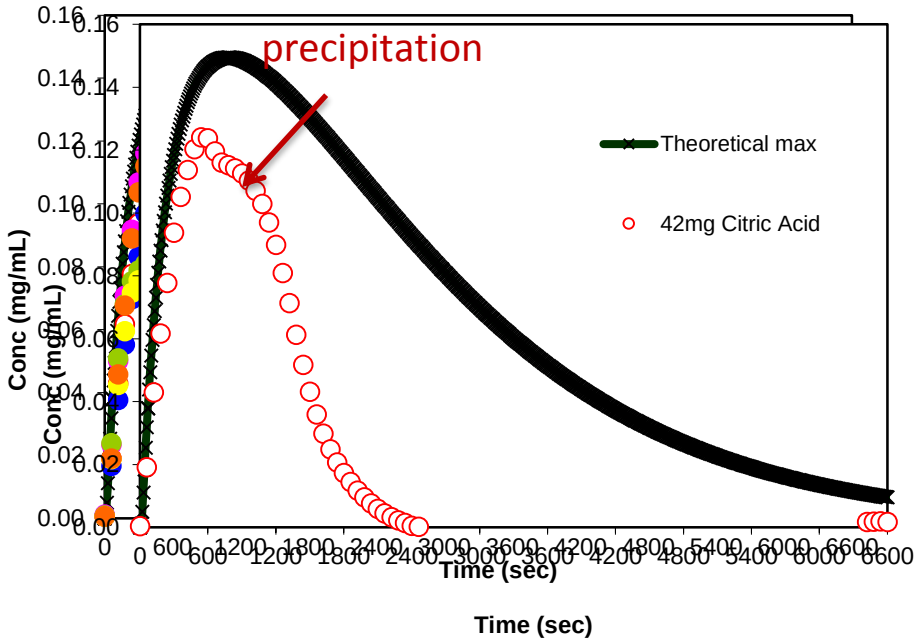


Experimental Results: concentration profiles

Gastric concentration profiles



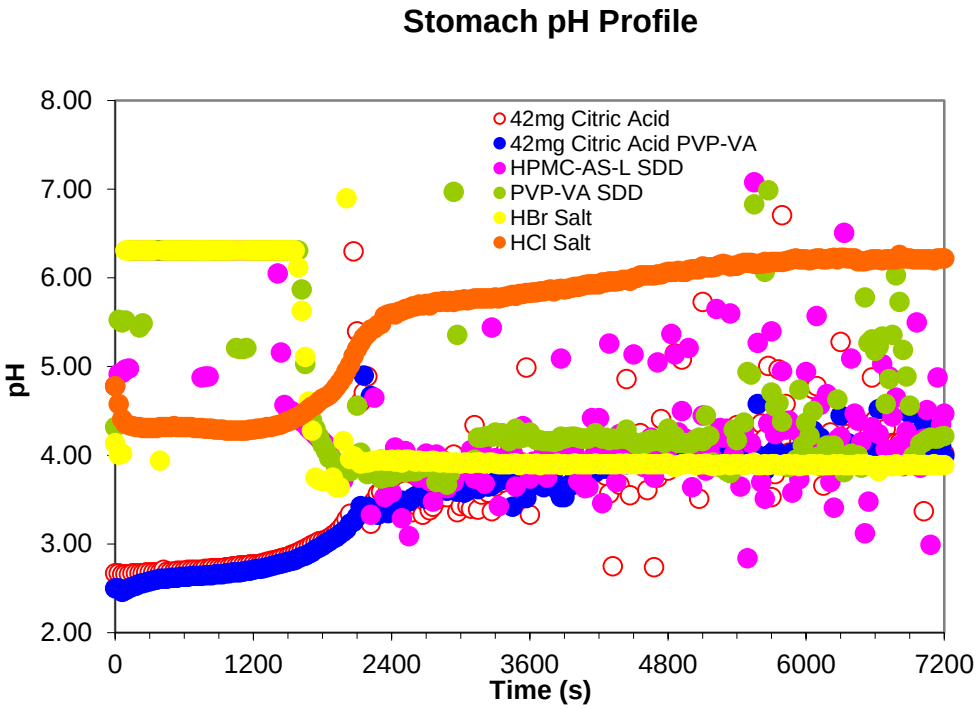
Duodenal concentration profiles

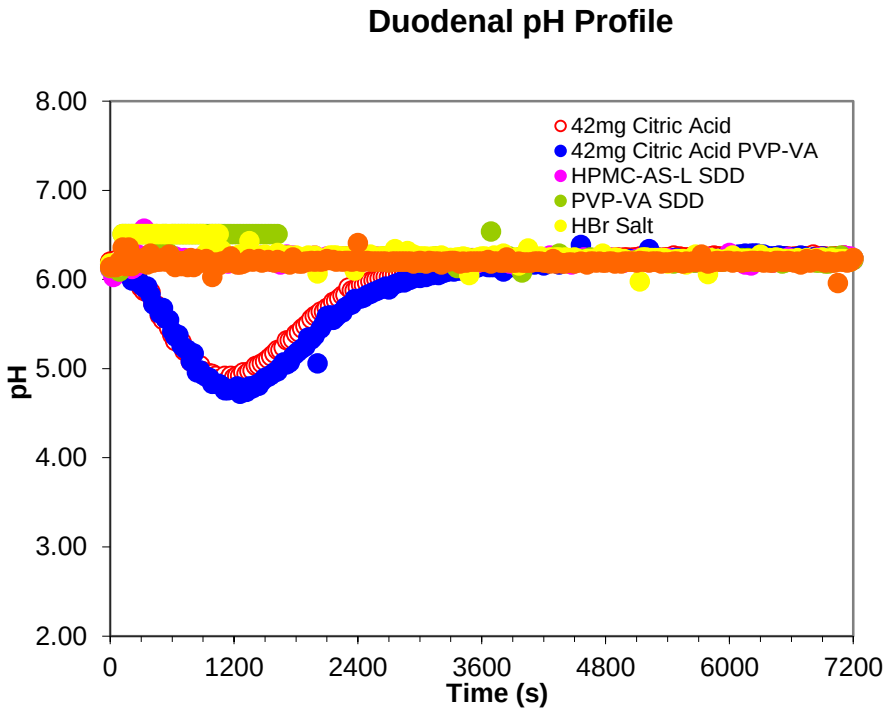


Case studied: compound + citric acid

Lee Burns

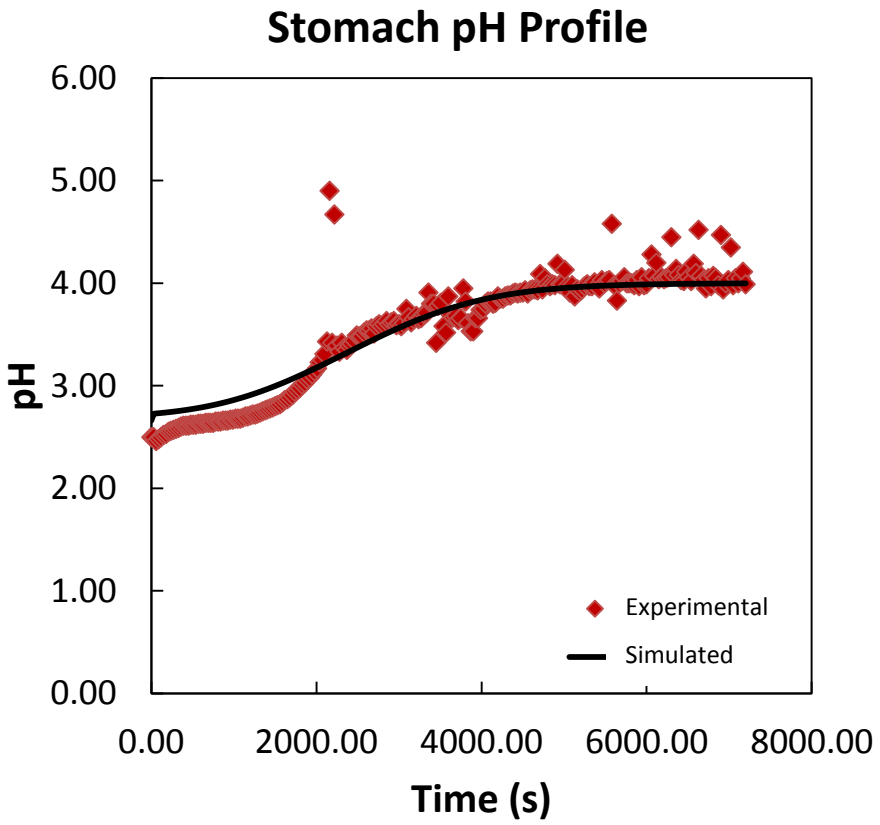
Experimental Results: pH profiles

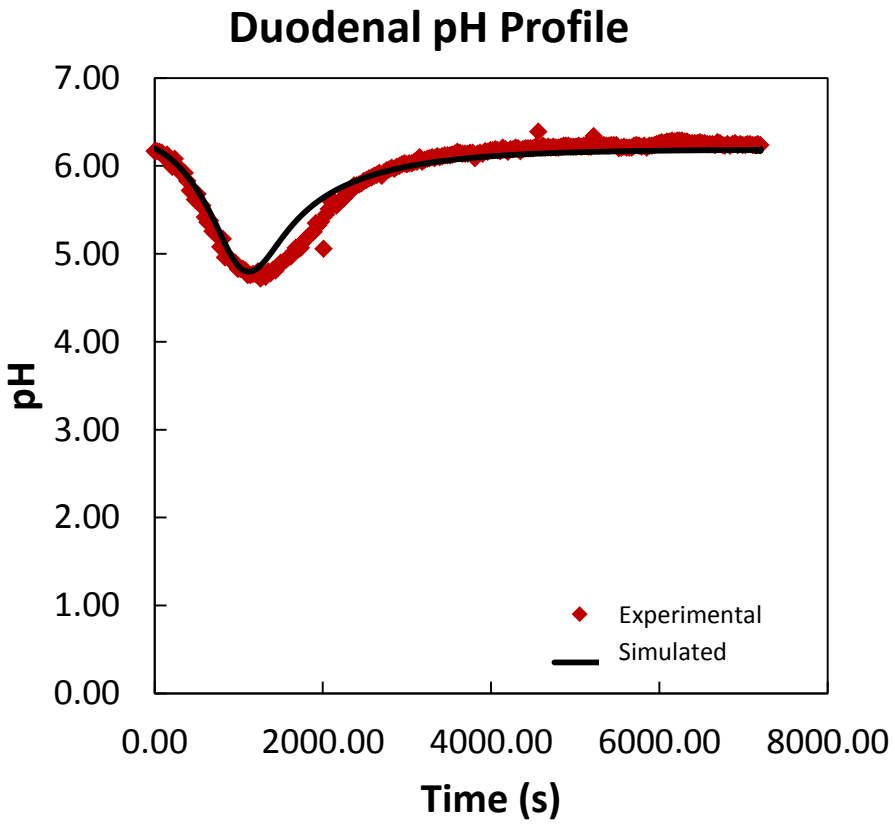




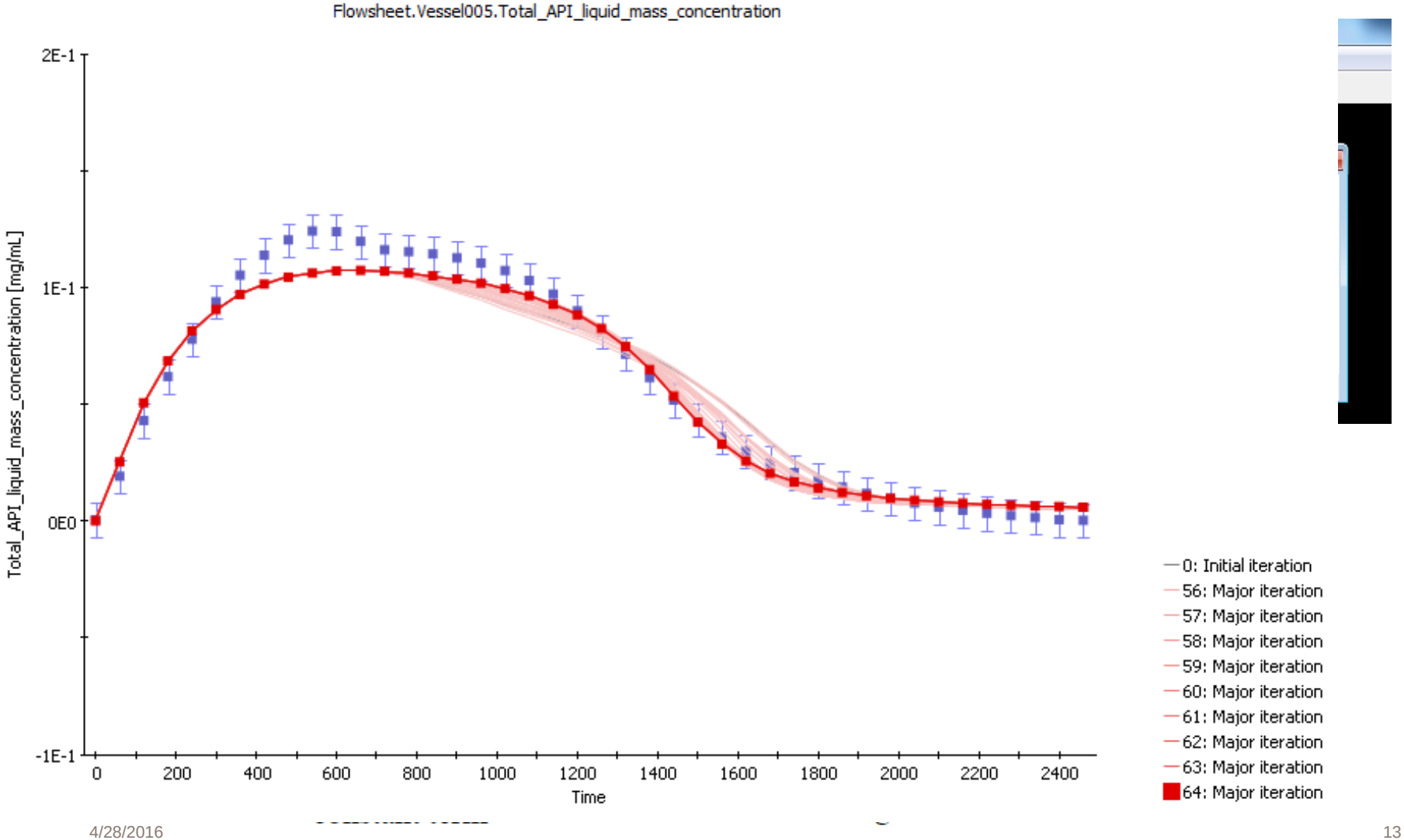
Lee Burns

Experimental Results: pH profiles

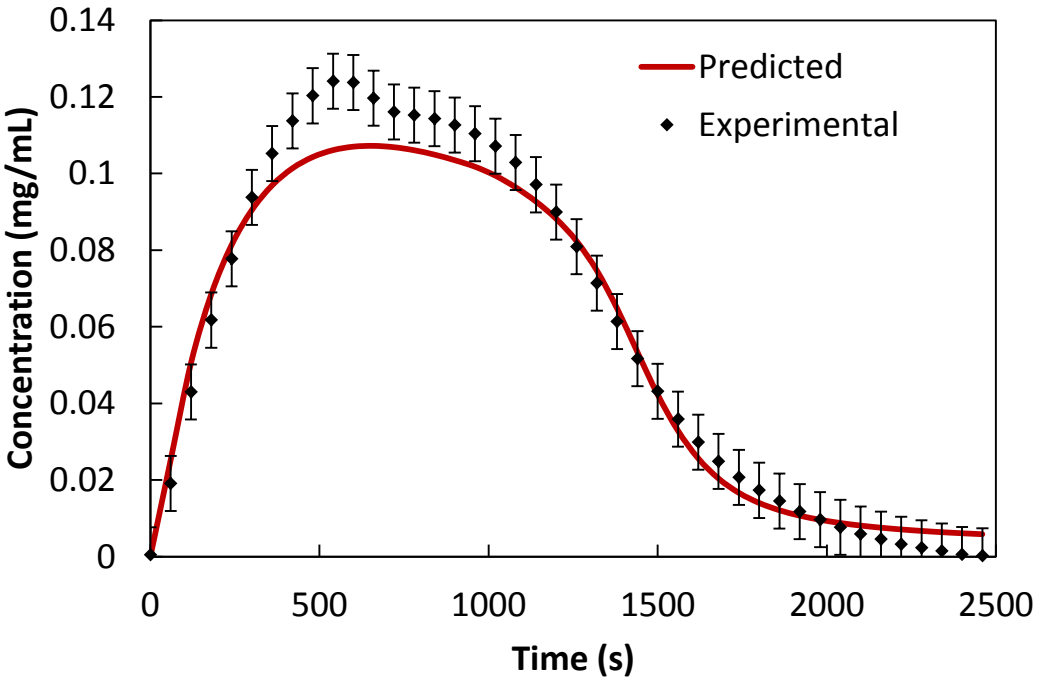




Estimating precipitation kinetics



Simulation results

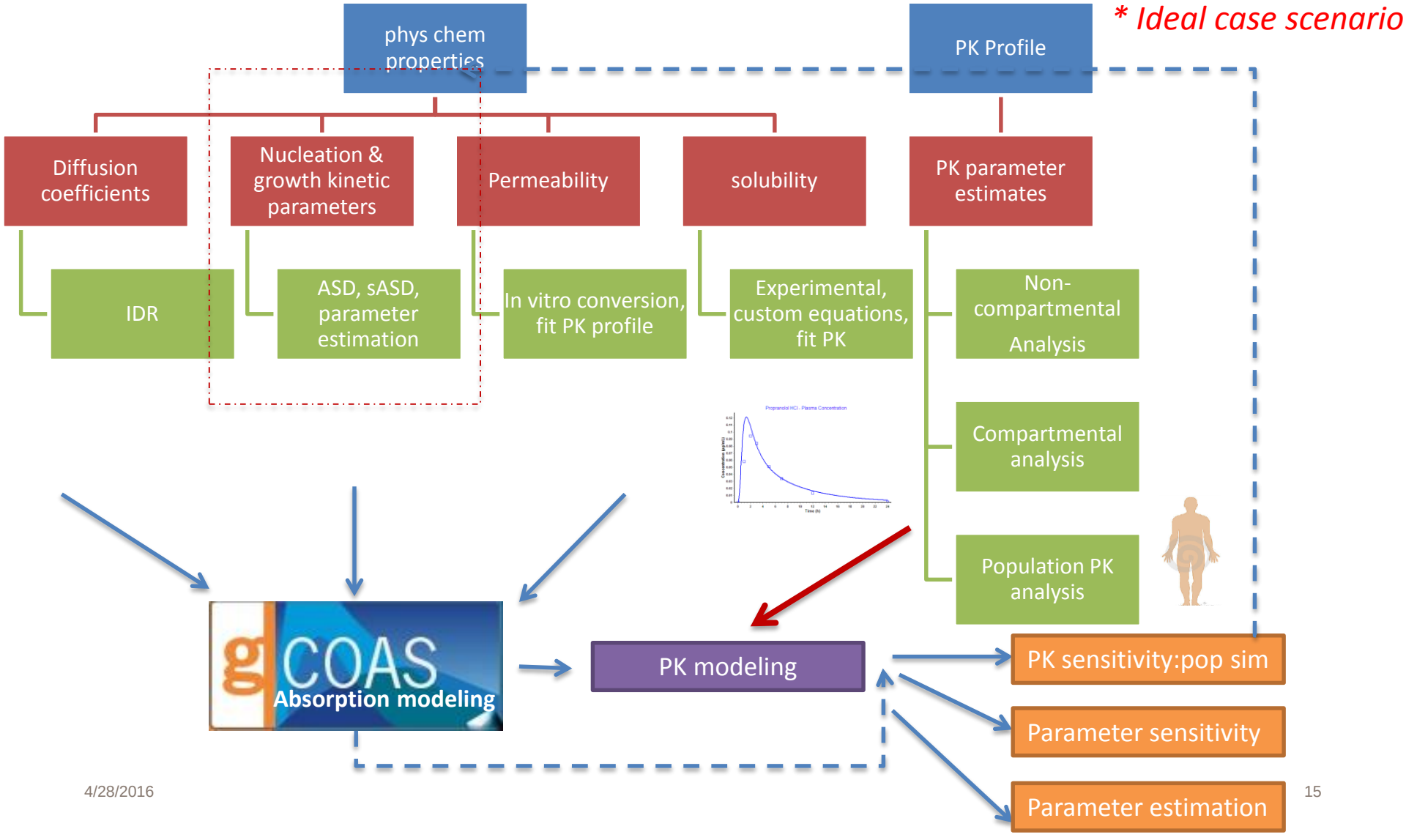


Lack of fit test:

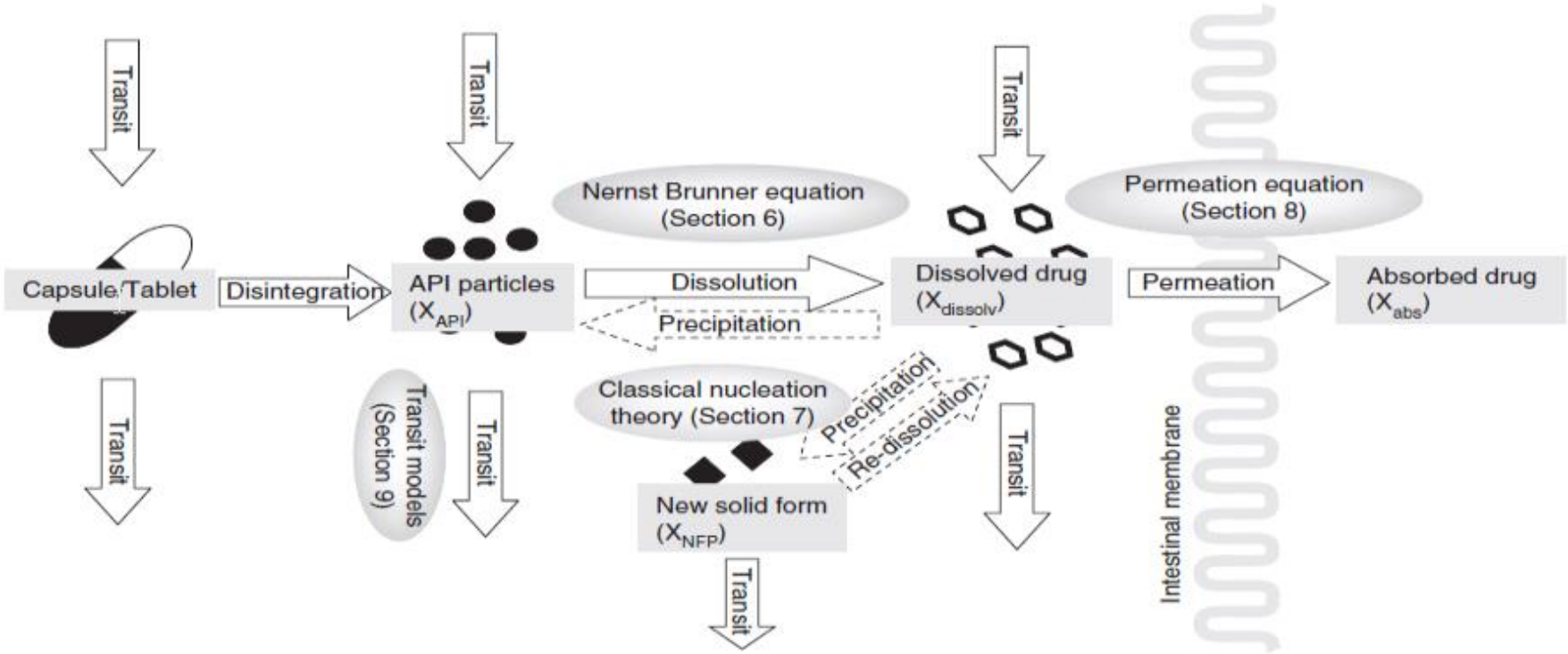
Weighted residual	χ^2 *value* (95%)
42.33	52.19

Model parameter	Final value	Initial guess	95% C.I	Standard deviation
Growth constant	0.55	0.36	1.42	0.70
Growth order	1.60	0.81	2.29	1.13
Nucleation coefficient	14.01	13.85	974.9	481.2
Nucleation order	2.61	2.77	399.3	197.1

Work flow of oral absorption modeling using gCOAS



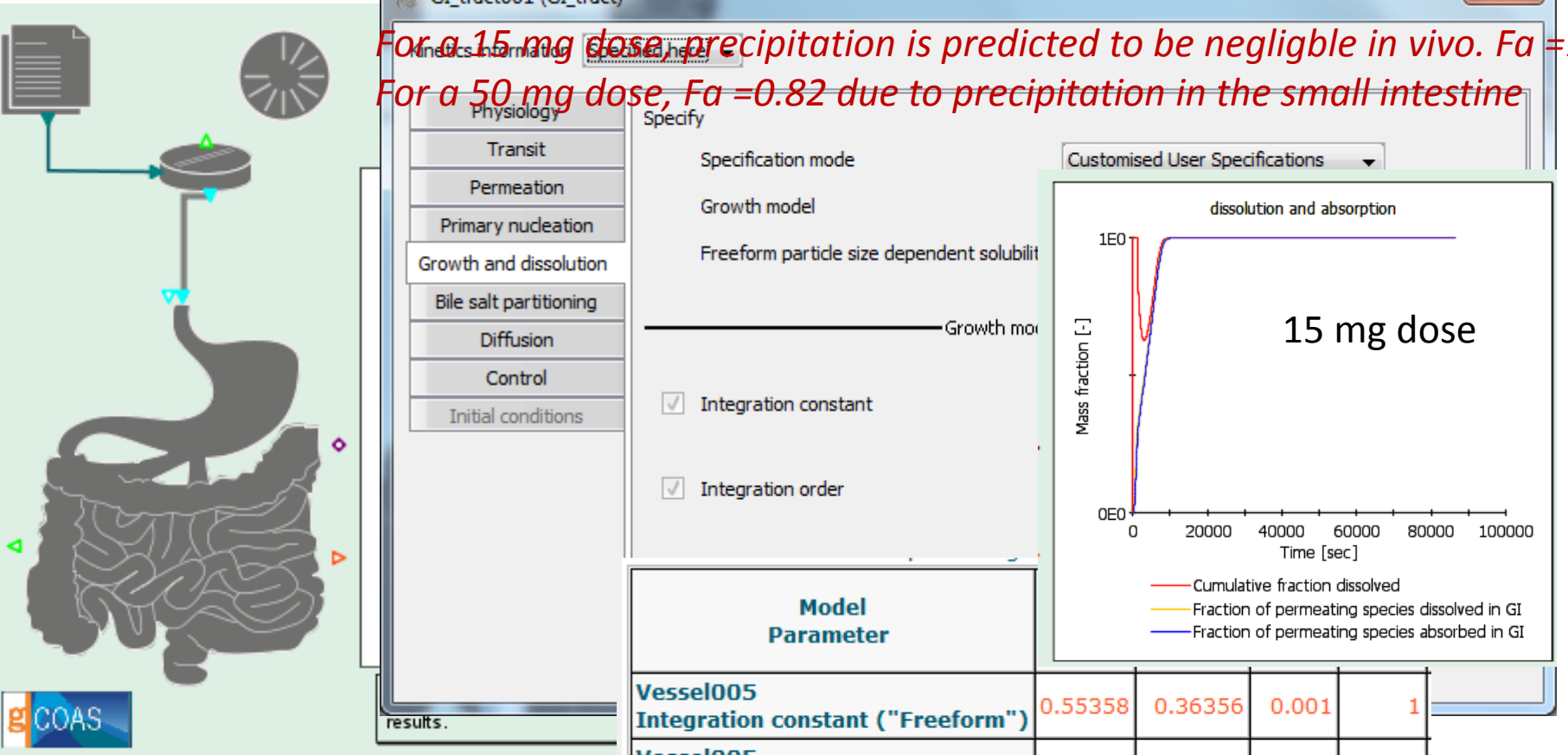
A gPROMS-based Computational Oral Absorption Simulation Framework



K. Sugano, *Expert Opin. Drug Metab. Toxicol.* (2009) **5**(3), pp. 259-293

Incorporating ASD results in gCOAS GI model

For a 15 mg dose, precipitation is predicted to be negligble in vivo. Fa =1
For a 50 mg dose, Fa =0.82 due to precipitation in the small intestine



Model Parameter				
Vessel005 Integration constant ("Freeform")	0.55358	0.36356	0.001	1
Vessel005 Integration order ("Freeform")	1.59909	0.814145	0.8	2
Vessel005 Rate constant ("Freeform")	14.0132	13.8547	0.0001	20
Vessel005 Order ("Freeform")	2.60956	2.77297	1	5

Property	Value at time 86400.0
Cumulative fraction dissolved("Freeform")	0.8
Cumulative fraction absorbed	0.8

86400.0	Units
1.0	-
1.0	-

Final remarks

- The gCOAS ASD framework allows to extract quantitative precipitation kinetic parameters from ASD data
- The kinetic parameters for precipitationin can be integrated in the gCOAS oral absorption model to better understand the impact of precipitation on bioavailability
- The ASD setup along with the gCOAS tools can further help investigate the impact of bile salts and pH on precipitation
- Custom precipitation kinetics can allow to account for changes in physiology (pH, bile concentration) on nucleation and growth