Supp. Info. for "Process-based modelling of microbial community dynamics in the human colon"

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1 Mathematical Model

1.1 Simple Model

In this section we present a very simple model with one microbial group and one colon compartment that we then use to derive bounds on parameters (e.g. absorption of SCFA and water) and to look at the bulk properties of the system, e.g. the relationship between transit time and SCFA concentration.

This simple model consists of, bacteria (X), substrate (S), SCFA mass (Z) and water (W) all with units of mass. We set f_s as the fraction of the waste products of X that are SCFA, and Y is the amount of microbial growth for 1 g of S and a_Z and a_W are the absorption rates of Z and W. The rates of change are given by

$$\frac{dX(t)}{dt} = G(t)X(t) - X(t)V \tag{1}$$

$$\frac{dS(t)}{dt} = \dot{S_{in}} - \frac{G(t)X(t)}{Y} - S(t)V \tag{2}$$

$$\frac{dZ(t)}{dt} = f_s\left(\frac{1}{Y} - 1\right)G(t)X(t) - (V + a_Z)Z(t) \tag{3}$$

$$\frac{dW(t)}{dt} = \dot{W_{in}} - (V + a_W)W(t) \tag{4}$$

where microbial growth, G, is given by

$$G(t) = G^m \frac{S(t)}{S(t) + K} \tag{5}$$

where K is the half-saturation constant and G^m is the maximum growth rate of X on S. Transit time is incorporated via the washout rate, V such that $V = 1/T_t$.

Steady state analysis (i.e. when the system is not changing with time) of the one group model can be used to give us some bounds or checks on the bulk properties of the system. The steady state solution (at time, t_s), assuming $X > 0$, is given by

$$X(t_s) = (\dot{S_{in}}/V - S(t_s))Y \tag{6}$$

$$S(t_s) = \frac{VK}{G^{\max} - V} \quad (7)$$

$$Z(t_s) \approx VX(t_s)\frac{1-Y}{Y(a_Z + V)} \quad (8)$$

$$W(t_s) = \frac{\dot{W_{in}}}{a_W + V} \quad (9)$$

where $\dot{X_{in}}$ is the inflow rate of X.

1.2 Microbial yield and substrate inflow

Assuming the microbes consume all available substrate, then the steady state mass of microbes can be approximated by

$$X(t_s) \approx \frac{\dot{S_{in}}Y}{V} \quad (10)$$

where $\dot{S}_{in}$ is the dietary inflow of all substrates (i.e. dietary P, C and mucin); V is the wash out rate from the system and Y, the microbial yield. Assuming the output of microbes (given by $X_{t_s}V$) is 14-28 g d^{-1} (Stephen and Cummings, 1980) (with midpoint of 21) and the substrate inflow is about 65 g d^{-1}; Eq. 10 suggests that Y is 21/65 i.e. about 0.3 which matches very well with the yield values for our functional groups which have yield values around 0.28 or 0.33 (see other Supp. Info. file).

1.3 Specific water absorption, a_W

Extending Eq. 9 to N compartments with downstream flow from 1 to N, and assuming the specific absorption rate is the same in all, then at steady state the water in each compartment is given by,

$$W_1 = \frac{\dot{W_{in}}}{a_W + V_1}, \quad (11)$$

$$W_2 = \frac{W_1 V_1}{a_W + V_2}, ... \quad (12)$$

$$..., W_N = \frac{W_{N-1}V_{N-1}}{a_W + V_N} \quad (13)$$

Successively substituting for the unknowns gives

$$W_N = \frac{\dot{W_{in}}V_1 V2...V_{N-1}}{(a_W + V_1)(a_W + V_2)...(a_W + V_N)} \quad (14)$$

If 90% of water is absorbed over the transit time then in the last compartment, N, $W_N V_N = 0.1\dot{W_{in}}$. Substituting this into Eq. 14 gives

$$\prod_{k=1}^{N}(a_W + V_k) = 10\prod_{j=1}^{N} V_j. \quad (15)$$

This can be solved numerically where V_j is computed by dividing the colon into N compartments which each take fraction, f_j^T, of the total transit time to pass

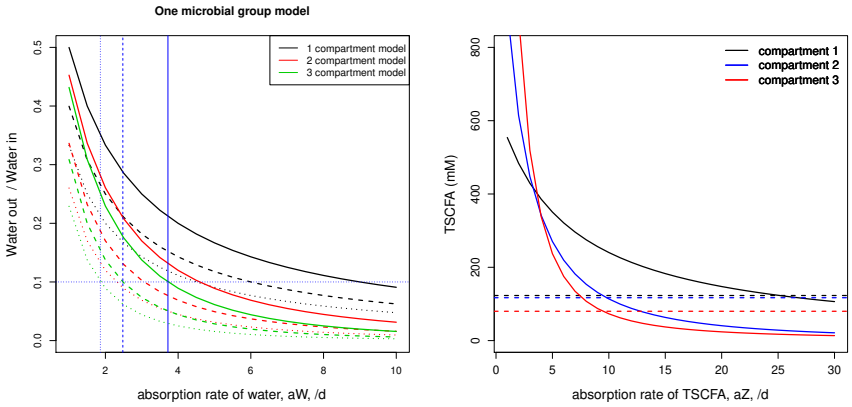

Figure S1: a) Achieving 90% water absorption for different transit times (1, 1.5 and 2 days represented by solid, dashed and dotted line respectively) and different number of compartments (1, 2, and 3 by colour, as shown in legend). The dotted horizontal line shows the required value for 90% incoming water absorption in the colon and the vertical blue lines show the a_W value which gives the correct total absorption for the 3 different transit times (which are as before, 1, 1.5 and 2 days represented by solid, dashed and dotted line respectively). b) Investigating SCFA absorption. TSCFA (mM) for different a_Z for transit time of 1.25 days, for the one group, three compartment model. a_Z is from 1,2,...30 /d with values constant throughout the colon. The dashed horizontal lines show the expected TSCFA in each compartment. The simulation is for 5 days and the results are the mean over the last day. Constant inflow and outflow (no meals or bowel movements) with a_W changing with transit time according to Eq. 16.

through. Using fractional times based on compartment volume (Fig. 1 in main manuscript) and assuming that a_W is the same in each compartment we find that for a one compartment model, $a_W = \frac{9}{T_t}$; for a two compartment model, $a_W = \frac{4.59}{T_t}$; and for a three compartment model, $a_W = \frac{3.72}{T_t}$ (see Fig. S1). This can be expressed exactly by

$$a_W = \frac{16.95 - 9.72N + 1.77N^2}{T_t} \tag{16}$$

where N is the number of compartments in the model. Note that this does not mean that specific water absorption changes with transit time, rather that to fulfill the 90% absorption criteria we can set a_W based on N and T_t. Once a typical transit time is chosen, the value of a_W can be fixed. As a rough estimation, $a_W \approx 3$ /d for a 3 compartment model with a transit time between one to one and a half days (Fig. S1). Given this will not be significantly affected by the microbial model (microbial uptake/production of water is small) this result will apply to all of the models in this work.

1.4 Specific SCFA absorption, a_Z

Using our one group microbial group model but adapted for 3 compartments, and our estimation for a_W based on transit time and the number of compartments (Eq. 16), we run the model for a transit times of 1.25 d with continuous inflow and outflow, over a range of a_Z from 1-30 d^{-1}. We compute TSCFA from our model by converting Z from g to mM using

$$Z_{mM} = 10^6 \frac{Z_g}{W_g m_Z} \tag{17}$$

where m_Z is computed by assuming TSCFA is in the ratio 3:1:1 (Ac:Bu:Pr) to give a weighted mean molar mass of TSCFA, m_Z of 68.4 g mol^{-1}. Fig. S1, shows the TSCFA in each model compartment versus a_Z. The horizontal dashed lines show the TSCFA value matching the model criteria, indicating the best estimates were a_Z equal to 25.2, 4.2 and 9.2 d^{-1} in the proximal, transverse and distal colon respectively. However, this was determined using a_Z constant through the colon so if a_Z varies between compartments this will change the results. In the interests of a robust model (i.e. the fewer parameter values, the better) we made the decision to use one value for a_Z . Given the experimental value of 9.6 d^{-1} compares well with our best estimate for the distal colon (9.2 d^{-1}) we decided to set aZ =9.6 d^{-1} throughout. It should be noted however that decreasing a_Z along the colon has been implemented in other models e.g. Labarthe et al. (2019).

2 Effect of Transit Time

Experimental evidence (e.g. (Lewis and Heaton, 1997)) shows that TSCFA (mM) decreases as transit time increases. We can explain why this is, mathematically, using a very simple one group model with monod growth, which we can solve analytically at steady state. To compute TSCFA in mM we need to use the fraction of P that is SCFA and then divide by the mean molor mass (m_m)and multiply by 1000 to find mmol. We then need to divide by W in litres, thus,

$$\text{TSCFA} = 10^6 \frac{P f_s}{W m_m} \tag{18}$$

Substituting for P and W, ignoring scaling constants and assuming remaining substrate at steady state is negligible, shows that TSCFA is linearly related to the expression

$$\frac{\dot{S_{in}}}{\dot{W_{in}}} \frac{a_W + V}{a_P + V} \tag{19}$$

To see the effect of simply changing the transit time through the colon on TSCFA we assume $\dot{S_{in}}$ and $\dot{W_{in}}$ are fixed and replace V by $1/Tt$ to get

$$TSCFA \propto \frac{a_W T_t + 1}{a_P T_t + 1} \tag{20}$$

Since we have a_W=3 and a_P=9.6, the denominator will increase much faster than the numerator as T_t increases thus, theoretically, TSCFA will decrease as transit time increases as SCFA are absorbed faster than water. Using realistic

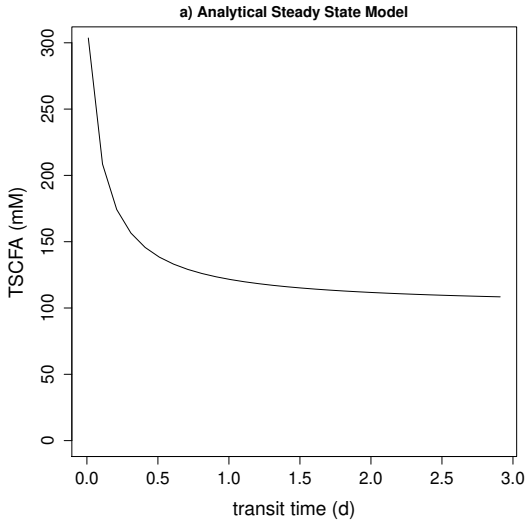

Figure S2: TSCFA as a function of transit time obtained from the solution of Eqs. 2-4. We convert from product mass, P, to moles using the average molar mass (weighted according to A:B:P = 3:1:1) of 68.5 g/mol and compute f_s as an average of the microPop microbial group stoichiometries to be approximately 0.5. We set inflowing substrate at 65 g/d (dietary substrate plus mucin) and inflowing water at 1100 g/d, with parameter values Y=0.3, $G^{\max}$=20 /d and K=0.001. [transitTimeModel.R]

parameter values in the above model (Eq. 2-4) allows us to plot TSCFA against transit time – see Fig S2 which compares very well with the experimental data shown in Fig. 1 by Lewis and Heaton (1997).

3 Microbial group parameter values

The parameters describing the different microbial groups are the same as the intrinsic functional groups given in the microPop R package (version 1.6), with one exception. We increased the maximum growth rate of Lactate Producers on RS from 6 d^{-1} to 7 d^{-1} and their pH tolerance were cordinates changed to tolerate lower pH (first two pH coordinates now 4.5 and 5.25, rather than 4.95 and 5.7) to ensure a better chance of their survival in the model. This section shows the data frames used for each microbial group in microPopGut. The following list explains the different entries in these data frames.

- 'Rtype' refers to the substrate type on the pathway:
  - 'X': not involved in pathway
  - 'S': substitutable substrate (this can be interchanged with other substitutable substrates)
  - 'Se': essential substrate (the microbes can not grow without this)
  - 'Sb': boosting substrate (if this is present the microbe can grow faster)

  - 'Sw': water
  - 'P': metabolic product

- 'halfsat' is the half saturation constant for monod growth
- 'yield' is the microbial mass produced from one gram of substrate
- 'maxGrowthRate' is the specific maximum growth rate of the microbes
- 'stoichiom' refers to the number of moles of each molecules involved in growth
- 'keyResource' is the substrate whose uptake rate is used to compute the uptake of the other substrates on the pathway according to the stoichiometry
- 'numPathways' defines how many metabolic pathways the microbial group has. When there is more than one pathway, numbered parameter names for the subsequent pathways are used.

For more details please refer to Kettle et al. (2015) and Kettle et al. (2018) or use the help function within the microPopGut package.

Table 1: Bacteroides

	units	Protein	NSP	RS	Acetate	Propionate	Succinate	H2	CO2	other
Rtype	none	X	S	S	P	P	P	P	P	X
halfSat	g/l		0.001	0.001						
yield	g/g		0.286	0.333						
maxGrowthRate	/d		12	24						
stoichiom	mol		2	2	2	1	1	2	1	
keyResource	none									
numPathways	none	2								
Rtype.2	none	S	X	X	P	P	P	P	P	P
halfSat.2	g/l	0.001								
yield.2	g/g	0.2								
maxGrowthRate.2	/d	24								
stoichiom.2	mol	6			2	1	1	2	1	7
keyResource.2	none									
pHcorners	pH	5.6	6.35	7.85	8.6					

Table 2: NoButyStarchDeg

	units	NSP	RS	Acetate	H2	CO2	H2O
Rtype	none	S	S	P	P	P	Sw
halfSat	g/l	0.001	0.001				
yield	g/g	0.286	0.333				
maxGrowthRate	/d	3.6	14.4				
stoichiom	mol	1	1	2	4	2	2
keyResource	none						
numPathways	none	1					
pHcorners	pH	5.35	6.1	7.6	8.35		

Table 3: NoButyFibreDeg

	units	NSP	RS	Acetate	Succinate	H2
Rtype	none	S	S	P	P	P
halfSat	g/l	0.001	0.001			
yield	g/g	0.286	0.333			
maxGrowthRate	/d	16.8	3.6			
stoichiom	mol	1	1	1	1	1
keyResource	none					
numPathways	none	1				
pHcorners	pH	5	5.75	7.25	8	

Table 4: LactateProducers

	units	NSP	RS	Sugars	Acetate	Lactate	Formate	Ethanol	H2O
Rtype	none	S	S	S	P	P	P	P	Sw
halfSat	g/l	0.001	0.001	0.001					
yield	g/g	0.286	0.333	0.333					
maxGrowthRate	/d	7.2	7	24					
stoichiom	mol	6	6	6	10	4	2	1	1
keyResource	none								
numPathways	none	1							
pHcorners	pH	4.5	5.25	7.2	7.95				

Table 5: ButyrateProducers1

	units	NSP	RS	Sugars	Acetate	Butyrate	H2	CO2	H2O
Rtype	none	S	S	S	Sb	P	P	P	P
halfSat	g/l	0.001	0.001	0.001	0.001				
yield	g/g	0.286	0.333	0.333					
maxGrowthRate	/d	8.4	8.4	24					
stoichiom	mol	2	2	2	2	3	2	4	2
keyResource	none	Hex							
numPathways	none	1							
nonBoostFrac	none	0.75							
pHcorners	pH	4.95	5.7	7.2	7.95				

Table 6: ButyrateProducers2

	units	NSP	RS	Sugars	Acetate	Butyrate	Lactate	Formate	CO2	H2O
Rtype	none	S	S	S	Sb	P	P	P	P	P
halfSat	g/l	0.001	0.001	0.001	0.001					
yield	g/g	0.286	0.333	0.333						
maxGrowthRate	/d	14.4	7.2	24						
stoichiom	mol	6	6	6	4	7	2	6	4	4
nonBoostFrac	none	0.1								
keyResource	none	Hex								
numPathways	none	1								
pHcorners	pH	4.85	5.6	7.1	7.85					

Table 7: PropionateProducers

	units	NSP	RS	Sugars	Acetate	Propionate	CO2	Lactate	H2O
Rtype	none	S	S	S	P	P	P	X	P
halfSat	g/l	0.001	0.001	0.001					
yield	g/g	0.286	0.333	0.333					
maxGrowthRate	/d	7.2	7.2	24					
stoichiom	moles	3	3	3	2	4	2		2
keyResource	none								
numPathways	none	2							
Rtype.2	none	X	X	X	P	P	P	Se	P
halfSat.2	g/l							0.001	
yield.2	g/g							0.111	
maxGrowthRate.2	/d							4.8	
stoichiom.2	moles				1	2	1	3	1
keyResource.2	none	Lactate							
pHcorners	pH	4.75	5.5	7	7.75				

Table 8: ButyrateProducers3

	units	NSP	RS	Sugars	Acetate	Butyrate	Formate	H2	CO2	Lactate	H2O
Rtype	none	S	S	S	P	P	P	P	P	X	Sw
halfSat	g/l	0.001	0.001	0.001							
yield	g/g	0.286	0.333	0.333							
maxGrowthRate	/d	7.2	7.2	24							
stoichiom	mol	10	10	10	2	9	12	10	8		2
keyResource	none										
numPathways	none	2									
Rtype.2	none	X	X	X	Se	P	X	P	P	Se	P
halfSat.2	g/l				0.001					0.001	
yield.2	g/g									0.111	
maxGrowthRate.2	/d									4.8	
stoichiom.2	mol				2	3		2	4	4	2
keyResource.2	none	Lactate									
pHcorners	pH	4.85	5.6	7.1	7.85						

Table 9: Acetogens

	units	NSP	RS	Sugars	Acetate	H2	CO2	Formate	H2O
Rtype	none	S	S	S	P	X	X	X	X
halfSat	g/l	0.001	0.001	0.001					
yield	g/g	0.286	0.333	0.333					
maxGrowthRate	/d	7.2	7.2	24					
stoichiom	moles	1	1	1	3				
keyResource	none								
numPathways	none	3							
Rtype.2	none	X	X	X	P	Se	Se	X	P
halfSat.2	g/l					0.001	0.001		
yield.2	g/g						0.03		
maxGrowthRate.2	/d						2.4		
stoichiom.2	moles				1	4	2		2
keyResource.2	none	CO2							
Rtype.3	none	S	S	S	P	P	P	Se	X
halfSat.3	g/l	0.001	0.001	0.001				0.001	
yield.3	g/g	0.286	0.333	0.333					
maxGrowthRate.3	/d	7.2	7.2	24					
stoichiom.3	moles	1	1	1	3	2	2	2	
keyResource.3	none	Hex							
pHcorners	pH	5.25	6	7.5	8.25				

Table 10: Methanogens

	units	H2	CO2	CH4	H2O	Formate
Rtype	none	Se	Se	P	P	X
halfSat	g/l	0.001	0.001			
yield	g/g		0.03			
maxGrowthRate	/d		2.4			
stoichiom	mol	4	1	1	2	
keyResource	none	CO2				
numPathways	none	2				
Rtype.2	none	X	P	P	P	Se
halfSat.2	g/l					0.001
yield.2	g/g					0.00724
maxGrowthRate.2	/d					2.4
stoichiom.2	mol		3	1	2	4
keyResource.2	none	Formate				
pHcorners	pH	5.25	6	7.5	8.25	

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