

# **GUTS, BUGS, AND DIETARY FIBER**

Investigating the colon-diet-flora system using modeling and simulation

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# OVERVIEW

- ▶ How diet impacts gut microbiota, and subsequently, how microbiota affects health, has been a topic of significant discussion for the past several years?
- ▶ Many hypotheses relating microbiota state to health concerns are prevalent:
  - ▶ neural developmental disorders (autism spectrum)
  - ▶ anxiety and depression
  - ▶ obesity
  - ▶ cancer

- ▶ The human colon is inherently difficult to investigate *in vivo* due to its physical inaccessibility.
  - ▶ Assessment is usually done using only the materials entering the digestive system through diet or exiting as feces.
- ▶ Large variability exists in microbiota composition between individuals and within a single person, posing clinical challenges.

# OVERVIEW

Experimental Tool	Microbial Ecology	Host Physiology	Experimental Control	Cost <sup>A</sup>
Clinical Trials	x	x	limited	very high
Animal Models	x	x	moderate	high
Reactor Systems	x		high	moderate
Mathematical Models <sup>B</sup>	x	x	complete	low

**A:** Cost includes financial considerations, as well as ethical concerns and experimental time.

**B:** Mathematical models will often focus on either microbial ecology or host physiology to ensure models maintain analytical value.

# RESEARCH OBJECTIVES

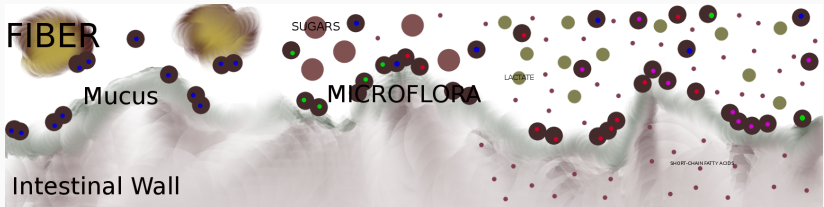
To design and develop a widely accessible software tool(s), grounded in physical modeling and deterministic approaches, to aid in exploring mechanical aspects of colon-diet-flora behavior through supporting the rapid design, execution and analysis of simulation experiments.

**COMPU** *GUT*

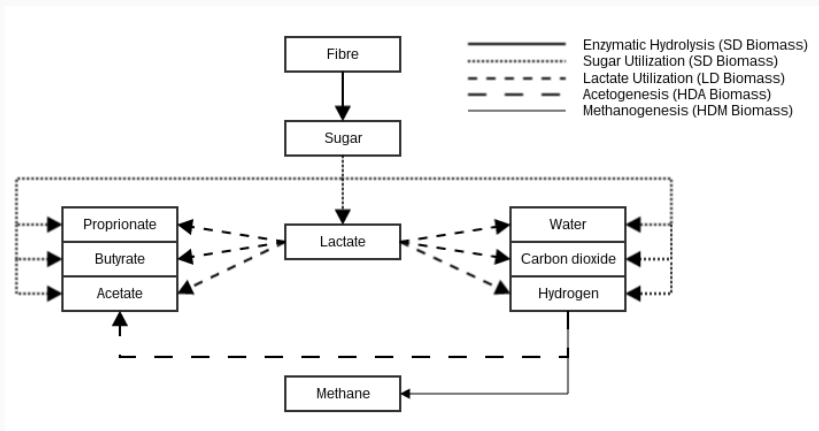
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<http://compugut.sourceforge.net>

# MATHEMATICAL FORMULATION

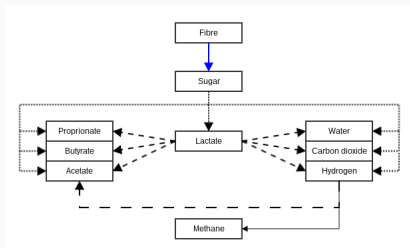


# MODEL





# MODEL



$$\phi_h = \mu \frac{F}{KX + F} X \quad (1)$$

$$\phi_f = \mu \frac{S}{K + S} X \quad (2)$$

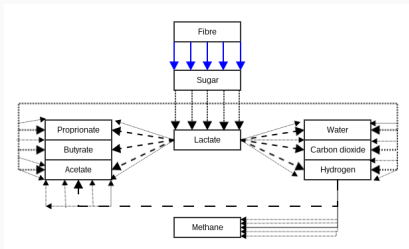
# MODEL

<i>For soluble components</i>											
$p_r$	Component i	1	2	3	4	5	6	7	8	9	Kinetic Rate
1	Hydrolysis	$S_1$	$S_2$	$S_3$	$S_4$	$S_5$	$S_6$	$S_7$	$S_8$	$S_9$	$\phi_1(c)$
2	Glucose utilization	$Y_{1,1}$	$Y_{2,2}$	$Y_{3,2}$	$Y_{4,2}$	$Y_{5,2}$	$Y_{6,2}$		$Y_{8,2}$	$Y_{9,2}$	$\phi_2(c)$
3	Lactate utilization	-1	-1	$Y_{3,3}$	$Y_{4,3}$	$Y_{5,3}$	$Y_{6,3}$		$Y_{8,3}$	$Y_{9,3}$	$\phi_3(c)$
4	Homoacetogenesis			-1	$Y_{4,4}$				$Y_{8,4}$	$Y_{9,4}$	$\phi_4(c)$
5	Methanogenesis			-1				$Y_{7,5}$	$Y_{8,5}$	$Y_{9,5}$	$\phi_5(c)$

<i>For particulate components</i>							
j	Component i	10	11	12	13	14	Kinetic Rate
1	Hydrolysis	$I_1$	$X_1$	$X_2$	$X_3$	$X_4$	$\phi_1(c) = \kappa_1 \frac{I_1 X_1}{K_1 X_1 + I_1}$
2	Glucose utilization		$Y_{11,2}$				$\phi_2(c) = \kappa_2 \frac{S_1 X_1}{K_2 + S_1}$
3	Lactate utilization			$Y_{12,3}$			$\phi_3(c) = \kappa_3 \frac{S_2 X_2}{K_3 + S_2}$
4	Homoacetogenesis				$Y_{13,4}$		$\phi_4(c) = \kappa_4 \frac{S_3 X_3}{K_3 + S_3}$
5	Methanogenesis					$Y_{14,5}$	$\phi_5(c) = \kappa_5 \frac{S_3 X_4}{K_5 + S_3} I_{pH}$
							with $I_{pH} = \begin{cases} \exp(-3(\frac{pH - pH_U}{pH_U - pH_L})^2) & \text{if } pH < pH_U \\ 1 & \text{if } pH \geq pH_U \end{cases}$
6	Decay of $X_1$		-1				$\phi_6(c) = \kappa_{6,1} X_1$
7	Decay of $X_2$			-1			$\phi_7(c) = \kappa_{7,1} X_2$
8	Decay of $X_3$				-1		$\phi_8(c) = \kappa_{8,1} X_3$
9	Decay of $X_4$					-1	$\phi_9(c) = \kappa_{9,1} X_4$

# MODEL

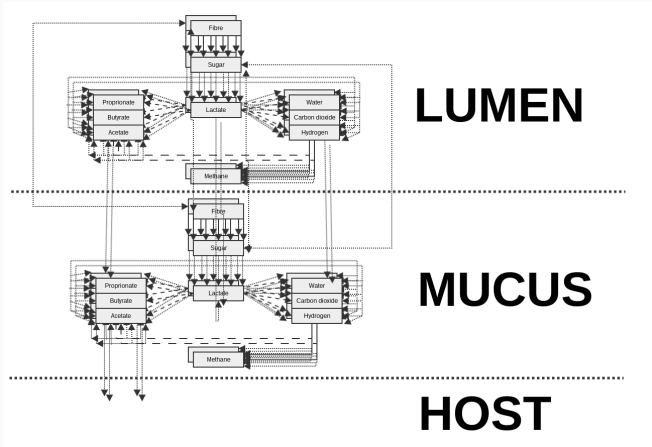


$$P_{i,j} = \mathcal{N}(P_i, \sigma)$$

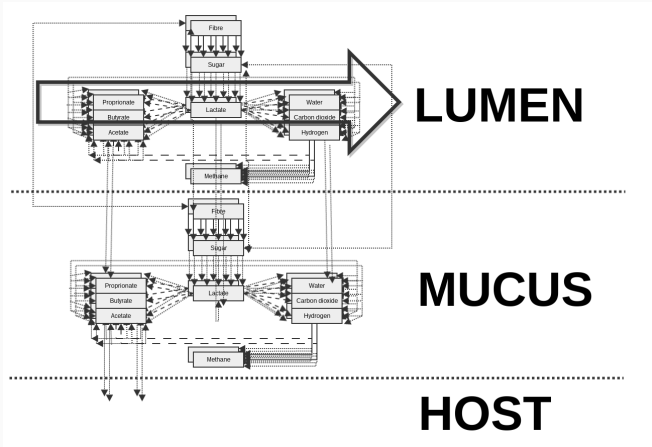
$$\phi_h = \frac{F}{F + \sum_i^n K_i X_i} \sum_i^n \mu_i X_i \quad (3)$$

$$\phi_f = \sum_i^n \mu_i \frac{S}{K_i + S} X_i \quad (4)$$

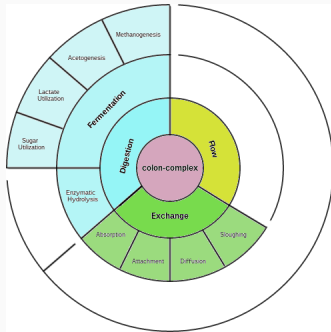
# MODEL



# MODEL



# MODEL



$$\partial_t \mathbf{c} + \partial_x f(\mathbf{c}) = r(\mathbf{c}) + e(\mathbf{c}) \quad (5)$$

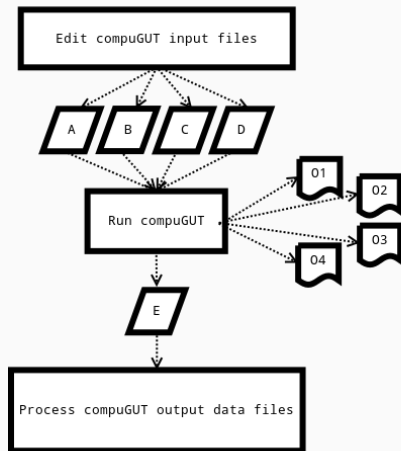
where  $\mathbf{c}$  = concentration of materials in the colon-complex

1. sugar
2. lactate
3. hydrogen
4. acetate
5. propionate
6. butyrate
7. methane
8. carbon dioxide
9. water
10. fiber
11. sugar utilizing biomass
12. lactate utilizing biomass
13. acetogenic biomass
14. methanogenic biomass

## System Details

<b>Process Model:</b>	colon-complex (diet-flora-colon)
<b>Sub-processes:</b>	3
<b>Number of State Variables:</b>	28-100
<b>Biochemical Parameters (BP):</b>	34
<b>Spatial Exchange Parameters (SEP):</b>	56
<b>Physical Parameters (PP):</b>	10
<b>Operation Parameters (OP):</b>	9

# COMPUGUT



A = Operation Instructions  
B = Diet Specifications  
C = Inoculation Conditions  
D = ADM1 Parameters

O1 = Simulation Summary  
O2 = Simulation Parameters  
O3 = Recorded Time Values  
O4 = Colon Input Fiber v Time

E = Output Data Files



```

# compuGUT: Operation Instructions
# Created: June 28th, 2014

# Simulation Type:
1.0      p0 - Simulation Type (1: continuous, 2: 3-stage, 3: gradostat, 4: All [for comparison])

# Sizing and Operation Parameters:      Values from www.webMD.com (Jun 28, 2014)
1.524   p1 - Length of colon [m]         - 5 feet in average human
0.0762  p2 - Average diameter of colon [m] - 3 inches in average human
6.096   p3 - Length of small intestine [m] - 20 feet in average human
0.0254  p4 - Average diameter of SI [m]   - 1 inch in average human

7.0     p5 - Average Flow rate [lpd]

28.0    p6 - Simulation Run Time [d]

# Microbial System:
1.0     p7 - Number of representative sugar degrading biomass species
1.0     p8 - Number of representative lactate degrading biomass species
1.0     p9 - Number of representative Hydrogen degrading acetogenic biomass
1.0     p10- Number of representative Hydrogen degrading methanogenic biomass
0.0     p11- Level of variance in which biological parameters may exist

# Sensitivity/Stability Parameters:
0.0     p12- Level of variance in which physical operations can exist

# Computing Parameters:
0.0     p13- Grid Resolution
10      p14- Number of Iterations between output save
-
-
-
-
-
-
"user operation instr compuGUT.txt" 29L, 1182C                                1,1                                All

```

```
compuGUT: In silico platform for simulation of intestinal fermentation  
Version: 0.1.0  
Copyright: 2015 Moorthy & Eberl
```

```
Problem Size: 28 x 51  
System Flow Rate [L/d]: 7.000000  
Convective velocity [m/d]: 1.534964  
Colon Volume [L]: 6.950000 (0.973000 + 1.946000 + 4.031000)  
Small Intestine Volume [L]: 3.088889  
delx = 0.030480 [m]  
delt = 0.019857 [d]
```

```
Simulating colon:  
Done!
```

```
compuGUT_fm Simulation Summary:  
Date and time: Fri Apr 3 23:38:01 2015
```

```
Simulation Type: Continuous Colon Model
```

```
Number of State Variables: 28  
Number of Sugar Degrading biomass: 1  
Number of Lactate Degrading biomass: 1  
Number of Acetogenic biomass: 1  
Number of Methanogenic biomass: 1  
Bioparameter variance: 0.000000
```

```
Grid resolution: 51  
Length of simulated colon [m]: 1.524000  
Average diameter of colon [m]: 0.076200  
Average flowrate [L/d]: 7.000000
```

```
Days simulated: 28.000000  
Computing time [s]: 190.610001  
Number of output files created: 1411
```

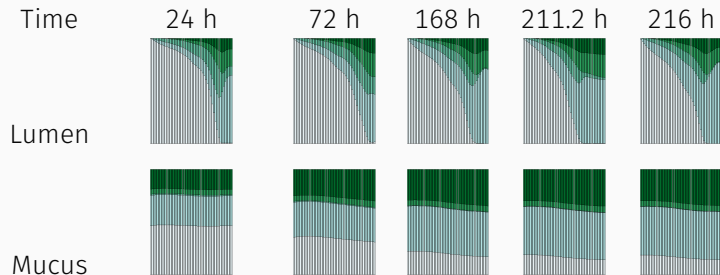
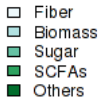
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Contact Arun [amoorthy@uoguelph.ca] or Hermann [heberl@uoguelph.ca] with questions or feedback
```

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(c) Moorthy and Eberl, 2015
```

```
SimulationSummary.txt (END)
```



# PRELIMINARY RESULTS



# PRELIMINARY SUMMARY

- ▶ Able to simulate a model system with primary substrate of fiber, nine subsequent substrates/metabolites, four biomass functional groups with up to ten subdivisions per group.
- ▶ We investigated how the colon microbiota composition varies as a result of three factors: (1) the total amount of fiber consumed, (2) the number of meals in which the fiber is distributed, and (3) the length/intensity of the meal.
  - ▶ The length of meal (15 minutes versus 30 minutes) has limited effect on the measured output.
  - ▶ Difference between measured output generated through a high-fiber diet and low-fiber diet simulation is amplified when meals are less frequent, and diminished when meals are consumed more frequently.

# PRELIMINARY SUMMARY

- ▶ Measurements of state variables vary along the length of the colon, suggesting that using single (CSTR-type) lumped assumptions may be inadequate.
- ▶ Overall system performance, judging how the anaerobic digestion process proceeds, during a period of distress is tempered by having a diverse microbial community present. However, the composition of the microbial community after a distress/perturbation period is often not the same as it was prior to that period.

# ANTIMICROBIAL EXTENSION

$$\partial_t A_1 + \bar{v}_l \partial_x A_1 = -Y_a \kappa_a \frac{A_1 X_1}{K_a + A_1} - \frac{\gamma_{3,a}}{V_l} (A_1 - A_2), \quad (6)$$

$$\begin{aligned} \partial_t X_1 + \bar{v}_l \partial_x X_1 &= Y_x \mu_f(S_1, X_1) - \left( \kappa_a \frac{A_1}{K_a + A_1} + \kappa_d + \gamma_{1,1} \right) X_1 \\ &\quad + \left( \frac{V_m}{V_l} \right) \gamma_{4,1} X_2, \end{aligned} \quad (7)$$

$$\partial_t A_2 = -Y_a \kappa_a \frac{A_2 X_2}{K_a + A_2} + \frac{\gamma_{3,a}}{V_m} (A_1 - A_2), \quad (8)$$

$$\begin{aligned} \partial_t X_2 &= Y_x \mu_f(S_2, X_2) - \left( \kappa_a \frac{A_2}{K_a + A_2} + \kappa_d + \gamma_{4,1} \right) X_2 \\ &\quad + \left( \frac{V_l}{V_m} \right) \gamma_{1,1} X_1, \end{aligned} \quad (9)$$



# ANTIMICROBIAL EXTENSION

For soluble components

	Component i	1	2	3	4	5	6	7	8	9	Kinetic Rate
$p_r$	Process	$S_1$	$S_2$	$S_3$	$S_4$	$S_5$	$S_6$	$S_7$	$S_8$	$S_9$	
1	Hydrolysis	$Y_{1,1}$									$\phi_1(c)$
2	Glucose utilization	-1	$Y_{2,2}$	$Y_{3,2}$	$Y_{4,2}$	$Y_{5,2}$	$Y_{6,2}$		$Y_{8,2}$	$Y_{9,2}$	$\phi_2(c)$
3	Lactate utilization		-1	$Y_{3,3}$	$Y_{4,3}$	$Y_{5,3}$	$Y_{6,3}$		$Y_{8,3}$	$Y_{9,3}$	$\phi_3(c)$
4	Homoacetogenesis			-1	$Y_{4,4}$				$Y_{8,4}$	$Y_{9,4}$	$\phi_4(c)$
5	Methanogenesis				-1			$Y_{7,5}$	$Y_{8,5}$	$Y_{9,5}$	$\phi_5(c)$

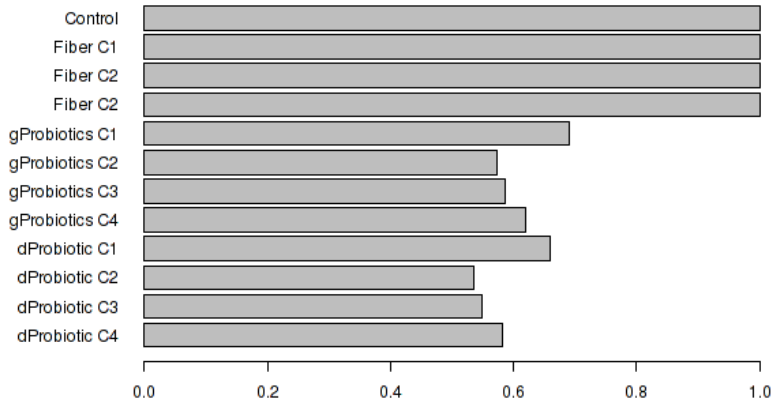
For particulate components

	Component i	10	11	12	13	14	15	Kinetic Rate
$j$	Process	$I_1$	$A_1$	$X_1$	$X_2$	$X_3$	$X_4$	
1	Hydrolysis	-1						$\phi_1(c) = \kappa_1 \frac{I_1 X_1}{K_1 X_1 + I_1}$
2	Glucose utilization			$Y_{11,2}$				$\phi_2(c) = \kappa_2 \frac{S_1 X_1}{K_2 + S_1}$
3	Lactate utilization				$Y_{12,3}$			$\phi_3(c) = \kappa_3 \frac{S_2 X_2}{K_3 + S_2}$
4	Homoacetogenesis					$Y_{13,4}$		$\phi_4(c) = \kappa_4 \frac{S_3 X_3}{K_3 + S_3}$
5	Methanogenesis						$Y_{14,5}$	$\phi_5(c) = \kappa_5 \frac{S_3 X_4}{K_5 + S_3} I_{pH}$
								with $I_{pH} = \begin{cases} \exp(-3(\frac{pH - pH_U}{pH_U - pH_L})^2) & \text{if } pH < pH_U \\ 1 & \text{if } pH \geq pH_U \end{cases}$
6	Decay of $X_1$			-1				$\phi_6(c) = \kappa_{6,1} X_1$
7	Decay of $X_2$				-1			$\phi_7(c) = \kappa_{7,1} X_2$
8	Decay of $X_3$					-1		$\phi_8(c) = \kappa_{8,1} X_3$
9	Decay of $X_4$						-1	$\phi_9(c) = \kappa_{9,1} X_4$
10	SAT		$Y_{11,10}$	-1				$\phi_{A,1}(c)$

# ANTIMICROBIAL EXTENSION

Sim No.	Category	Case	Description
1	Control	1	<i>compuGUT</i> is initially simulated for 14 days with standard diet from default initial conditions. After initial period, system receives 2.5 mL of targeted antibiotic every 4 hours for 5 days. After day 20, system is simulated at standard operating conditions for 312 days (recovery).
2	Fiber	1	Same as control, except following antibiotic treatment (day 20) fiber intake is increased to 40 g per meal for 10 days
3		2	Same as control, except following antibiotic treatment (day 20) fiber intake is increased to 80 g per meal for 10 days
4		3	Same as control, except following antibiotic treatment (day 20) fiber intake is increased to 40 g per meal for 20 days
5	Competitive Culture	1	except following antibiotic treatment (day 20) - 2 g/d of a generic probiotic supplement are consumed for a total period of 10 days
6		2	Same as control, except following antibiotic treatment (day 20) - 4 g/d of a generic probiotic supplement are consumed for a total period of 10 days
7		3	Same as control, except following antibiotic treatment (day 20) - 2 g/d of a generic probiotic supplement are consumed for a total period of 20 days
8		4	Same as control, except following antibiotic treatment (day 20) - a single 40 g dosage of a generic probiotic supplement is consumed
9	Flora re-compliment	1	Same as control, except following antibiotic treatment (day 20) - 2 g/d of a probiotic supplement designed to resemble a pre-treatment flora are consumed for a total period of 10 days
10		2	Same as control, except following antibiotic treatment (day 20) - 4 g/d of a probiotic supplement designed to resemble a pre-treatment flora are consumed for a total period of 10 days
11		3	Same as control, except following antibiotic treatment (day 20) - 2 g/d of a probiotic supplement designed to resemble a pre-treatment flora are consumed for a total period of 20 days
12		4	Same as control, except following antibiotic treatment (day 20) - a single 40 g dosage of a probiotic supplement designed to resemble a pre-treatment flora is consumed

# ANTIMICROBIAL EXTENSION



# ANTIMICROBIAL SUMMARY

- ▶ Simulation results suggest:
  - ▶ Dynamic effect of antimicrobial treatment varies between colon locations
  - ▶ Low dosages and short duration treatment regimes, though ineffective in eliminating the targeted biomass strain, alter the long-term composition of the microflora if there is no external intervention.
  - ▶ Probiotic-type intervention may be an effective method to improve rate of recovery after an unwanted shift in flora composition.

## CONCLUDING REMARKS

The compuGUT is very far from being a finished product. What has been demonstrated might best be described as foundational work. However, laying this foundation, the compuGUT, is an important initiative in promoting a sustainable modeling-experimental iterative approach, pushing forward for detailed understanding of the gut microbiota, its interactions, and impacts on health.

# ACKNOWLEDGMENTS

## Collaborators:

- ▶ Steve Brooks (Health Canada)
- ▶ Martin Kalmokoff (Agriculture Canada)
- ▶ Hermann Eberl (University of Guelph)
  - ▶ Jesse Knight
  - ▶ Kathleen Songin
  - ▶ Richard Yam

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For complete source see <http://compugut.sourceforge.net>.

QUESTIONS?