Journal of Theoretical Biology 266 (2010) 189–201

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Mathematical modelling of carbohydrate degradation by human colonic microbiota

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ARTICLE INFO

Article history:
Received 20 January 2010
Received in revised form
19 May 2010
Accepted 31 May 2010
Available online 16 June 2010

Keywords:
Anaerobic digestion
Colonic fermentation
Dynamic systems
Large intestine
Trophic chain

ABSTRACT

The human colon is an anaerobic ecosystem that remains largely unexplored as a result of its limited accessibility and its complexity. Mathematical models can play a central role for a better insight into its dynamics. In this context, this paper presents the development of a mathematical model of carbohydrate degradation. Our aim was to provide an *in silico* approach to contribute to a better understanding of the fermentation patterns in such an ecosystem. Our mathematical model is knowledge-based, derived by writing down mass-balance equations. It incorporates physiology of the intestine, metabolic reactions and transport phenomena. The model was used to study various nutritional scenarios and to assess the role of the mucus on the system behavior. Model simulations provided an adequate qualitative representation of the human colon. Our model is complementary to experimental studies on human colonic fermentation, which, of course, is not meant to replace. It may be helpful to gain insight on questions that are still difficult to elucidate by experimentation and suggest future experiments.

1. Introduction

The human colon (also called large intestine) is an anaerobic ecosystem within the gastrointestinal (GI) tract. It harbors an enormous number of microorganisms, which form the human colonic microbiota, a highly diverse community including more than 1000 microbial species (Rajilic-Stojanovic et al., 2007), mainly dominated by members of the bacterial phyla *Firmicutes* or *Bacteriodetes*. The domain *Archaea* also inhabits the human colonic ecosystem, with *Methanobrevibacter smithii* the dominant phylotype (Eckburg et al., 2005). This microbial community performs the breakdown of polysaccharides that are not digested in the upper intestine, mediating many of the effects of diet upon gut health (Flint et al., 2007). Fermentation produces essential vitamins and co-factors (Zoetendal et al., 2008), and contributes up to 10% of the energy of the body's metabolic requirements (Macfarlane and Cummings, 1991). The principal products of fermentation are short chain fatty acids (SCFA), microbial biomass, H_2, CO_2 (and CH_4 in some individuals). SCFA (mainly acetate, propionate and butyrate) are recognized for their health-promoting effects (Topping and Clifton, 2001).

Despite its important role in human health, the human colonic ecosystem remains largely unexplored due to the complexity of its microbiota. This dynamic microbial consortium is host-specific, and spatially distributed along the GI tract (Dethlefsen et al., 2006). Human *in vivo* studies are restricted by ethical considerations and the limited accessibility of the GI tract. These constraints have motivated the development of *in vitro* models to simulate the behavior of the human colon. The most sophisticated models in this category consist of series of well-mixed reactors that represent the physiological parts of the large intestine (Molly et al., 1994; Macfarlane, 1998). *In vitro* models have been particularly useful to investigate the carbohydrate fermentation of various substrates. However, most of them do not account for biotic factors such as SCFA absorption, interaction with the host, and exchange between the lumen and mucus microhabitats. In parallel to *in vitro* studies, animal models (mainly rodents and pigs) have also been used to investigate SCFA absorption (Fleming et al., 1991), spatial bacterial distribution (Sarma-Rupavtarm et al., 2004), and symbiotic host-bacterial relationships in the human GI tract (Samuel and Gordon, 2006; Mahowald et al., 2009).

Both *in vitro* and *in vivo* models have been crucial for the understanding of the human GI tract. Nevertheless, extrapolation of such studies to the human colon has to be done with caution.

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0022-5193/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2010.05.040

Animal intestines present physiological differences with the human colon. In addition, both *in vitro* and *in vivo* approaches use mixed culture of fecal matter, but only 20–40% of human colonic microbiota can be cultivated (Suau et al., 1999) and major differences have been found between fecal and colonic microbiota.

Mathematical modelling can complement *in vitro* and *in vivo* studies. It is a promising approach to circumvent some obstacles associated with experimental work. Although mathematical models have shown to be useful in animal nutrition (see, e.g., Dumas et al., 2008), up to now, they have rarely been used to study the complexity of the carbohydrate degradation in the human colon and few results have been reported in the literature. Mathematical approaches do not seem to have been applied to the study of the human colonic ecosystem as a whole. Only parts of the system have been considered. Studies in fermentation addressed the modelling of bacterial *in vitro* experiments and attempted to analyze specific reactions of the fermentation process by human colonic strains (Amaretti et al., 2007). Modelling studies based on ^{13}C-labelled carbohydrates have been used to evaluate fermentation in the small and large intestine of infants (Christian et al., 2002). Belenguer et al. (2006) also used labelled components to identify carbon flows in the metabolism of lactate-utilizing bacteria to produce butyrate. Such a metabolism is affected by exogenous acetate. Duncan et al. (2004) and Morrison et al. (2006) estimated, by modelling, the contribution of acetate in butyrate formation. Predictions given by these models are in good agreement with experimental data, and these models provide valuable insight on the structure and dynamics of human colonic microbiota, to be used in the construction of our model. Other phenomena taking place in the human colon have been studied by mathematical modelling. The colonization of microorganisms in the gut and dynamics of pathogens have received most attention (see, e.g., Kirschner and Blaser, 1995; de Jong et al., 2007). A mathematical approach was presented to describe the spatial distribution of intestinal bacteria with respect to their tolerance to oxygen, taking into account the variable geometry of the intestine (Wilkinson, 2002).

To the best of our knowledge, there is still no mathematical model integrating the physiology of the intestine, the carbohydrate fermentation process and mass transfer between the lumen and mucus. The purpose of the work reported in this paper was to develop such a mathematical model in order to provide a virtual platform describing the dynamics of the fermentation pattern in the human colon. We hope that the mathematical model presented here will contribute usefully to coping with the complexity of the human colon, enabling further insight into the microbial metabolism in the human GI tract.

This paper is organized as follows: Section 2 briefly describes the human colon. Section 3 presents the biological basis and assumptions under which our mathematical model is constructed. Section 4 details the model equations. Section 5 demonstrates how the model can be used to address questions and study scenarios that could not be tested otherwise. Model limitations and possible extensions are also described. The main conclusions of this work are in Section 6.

2. Description of the system

The human colon is a biochemical environment characterized by low redox potential and a constant controlled temperature of 37 °C (Savage, 1977). It consists of three well-defined anatomical regions, namely the proximal colon (cecum and ascending colon), the transverse colon and the distal colon (sigmoid and rectum). The colon receives food from the ileum. Some of it is retained in the proximal colon. The digesta (chyme) goes to the distal colon to be degraded or excreted.

Carbohydrates constitute 85% of available substrates for colonic fermentation. The substrates come mostly from the diet. Main dietary carbohydrates are resistant starch (RS) and non-starch polysaccharides (NSP). The pattern of fermentation products confers a spatial distribution of metabolites and a pH profile with values of about 5.5 in the proximal colon, 6.2 in the transverse colon and 6.9 in the distal colon (Macfarlane and Cummings, 1991).

The intestine is lined with the epithelium, where the secretion of a mucus gel layer is carried out by goblet cells. The mucus has the characteristics of a polymer-based matrix and allows the attachment of microorganisms and their resistance to shear forces. Mucus is mainly formed by mucins, which are high molecular weight glycoproteins with an important role in microbial development (Sonnenburg et al., 2004). The mucus is a carbon source that can support intestinal bacteria *in vivo* in the absence of any dietary input (Macfarlane and Cummings, 1991). Bacteria specialized in mucin degradation have been isolated (Salyers et al., 1977; Derrien et al., 2004).

As a consequence, within the large intestine, the human colonic microbiota is mainly located in two microhabitats, namely lumen and mucus. In terms of the bacterial species present, the predominant mucosa-associated population is distinct from the luminal one (Zoetendal et al., 2002; Eckburg et al., 2005).

3. Knowledge basis

The human colon can be viewed as a bioreactor. As chemical reactor models do, our mathematical model structure integrates a hydraulic representation of the system, and a description of the transport phenomena and reaction mechanisms. These three aspects are described below.

3.1. Hydraulic representation

A hydraulic representation of the human colon is displayed in Fig. 1. The three physiological regions described in the previous section are accounted for. In each of these regions, the lumen and mucus microhabitats are distinguished. Lumen and mucus compartments are described as continuous-flow stirred tank reactors (CSTR). The lumen reactors are connected in series. We assume that the compartments are completely mixed. This is partly justified by the presence of mixing forces such as peristaltic

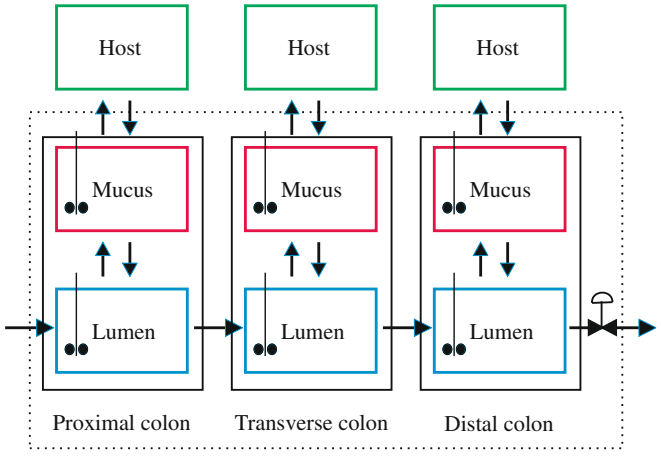

Fig. 1. Hydraulic representation of the human colon. The dotted rectangle represents the boundary of the system to be modelled.