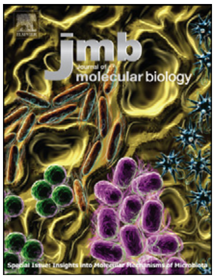

Towards Predictive Models of the Human Gut Microbiome

Vanni Bucci [1] **and Joao B. Xavier** [2]

*1 - **Department of Biology,** University of Massachusetts Dartmouth, 285 Old Westport Road, North Dartmouth, MA 02747, USA*
*2 - **Program in Computational Biology,** Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, Box 460, New York, NY 10065, USA*

***Correspondence to Vanni Bucci and Joao B. Xavier:** vbucci@umassd.edu; xavierj@mskcc.org*
http://dx.doi.org/10.1016/j.jmb.2014.03.017
Edited by Eric Martens

Abstract

The intestinal microbiota is an ecosystem susceptible to external perturbations such as dietary changes and antibiotic therapies. Mathematical models of microbial communities could be of great value in the rational design of microbiota-tailoring diets and therapies. Here, we discuss how advances in another field, engineering of microbial communities for wastewater treatment bioreactors, could inspire development of mechanistic mathematical models of the gut microbiota. We review the state of the art in bioreactor modeling and current efforts in modeling the intestinal microbiota. Mathematical modeling could benefit greatly from the deluge of data emerging from metagenomic studies, but data-driven approaches such as network inference that aim to predict microbiome dynamics without explicit mechanistic knowledge seem better suited to model these data. Finally, we discuss how the integration of microbiome shotgun sequencing and metabolic modeling approaches such as flux balance analysis may fulfill the promise of a mechanistic model.

Introduction

Mathematical models of multispecies microbial communities have a long tradition in design and control of environmental biotechnology processes. For more than 20 years, sophisticated mechanistic models have assisted engineers in understanding the relationship between operational parameters (e.g., flow rate, temperature and oxygenation) and microbial composition in wastewater treatment bioreactors [1]. Recent advances in metagenomics have reinforced the notion that the intestinal microbiome is composed of multiple microbial species in competition for limited nutrients and attachment sites and differentially susceptible to external perturbations, which is similar to bioreactors. Both the gut microbiota and wastewater have very high microbial biodiversity [2]. However, whereas the perturbations in bioreactors usually consist of changes in the operational variables such as flow rate of composition of the influent, in the microbiota, the perturbations are such as antibiotic treatment, changes in diet and exposure to external microbes (Fig. 1). There is a significant interest in optimal microbiome management due to its relevance to human health [3]. While most of our current insights come from experimental studies [4], it should be possible to develop mechanistically based mathematical models to assist in the design of intervention strategies, similarly to how engineers apply mathematical models in the design and management of bioreactors.

Mathematical Models in Environmental Biotechnology

Biological wastewater treatment is the process of clearing sewage water by converting the dissolved nutrients, which would otherwise cause eutrophication and bad water quality in the receiving water bodies, into microbial biomass, which can then be disposed or recycled. In these bioreactors, multispecies microbial communities grow by consuming carbon-, nitrogen- and phosphorus-rich organic compounds in the wastewater, effectively cleaning the water of these compounds. The microbial community can be very

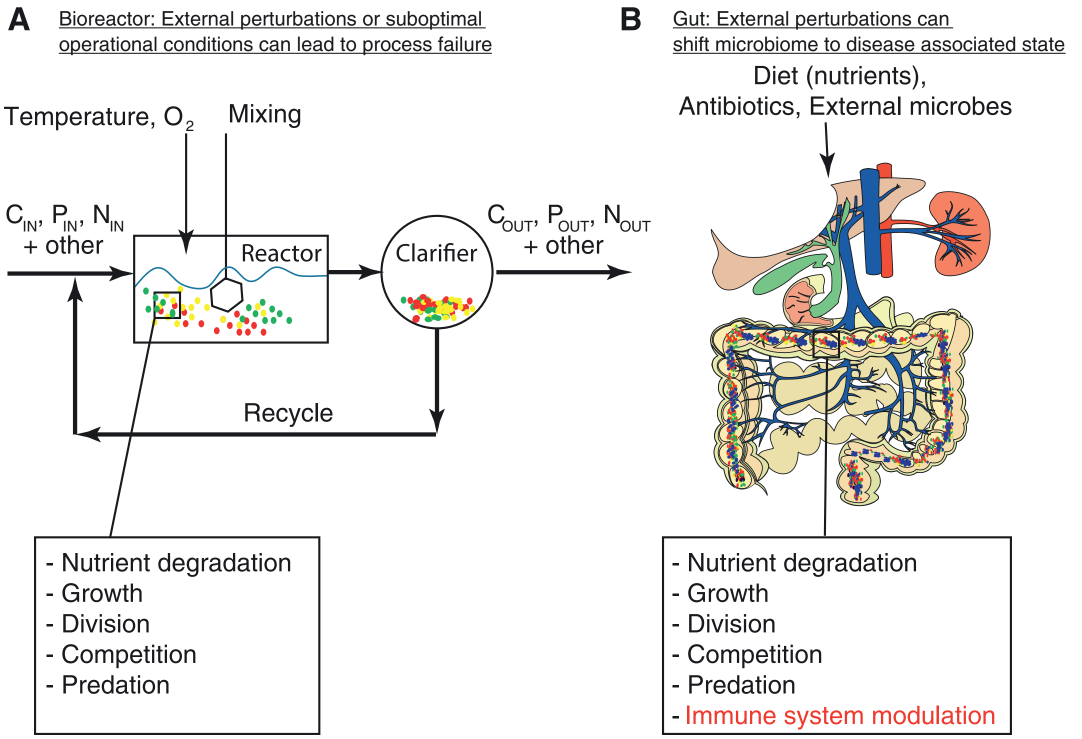

Fig. 1. Analogy between environmental engineering bioreactors and the human intestinal microbiome. Bioreactors, such as the activated sludge (A), use multispecies microbial communities to degrade waste (e.g., C = organic carbon) and other nutrients (e.g., N = nitrogen as ammonia, P = phosphorous) that if untreated can lead to environmental pollution problems. The optimal microbial community is selected by the bioengineer by tuning external parameters such as mixing, aeration and temperature. Composition shifts due to improper operational conditions can lead to system failure. (B) The intestinal microbiome is the multispecies microbial communities harbored in the human intestine. Similar to the environmental bioreactor communities, the microbiome degrades nutrients and is susceptible to external perturbations such as diet change and antibiotic application. Its composition shifts due to changes in diet or antibiotic use, and some community alterations have been associated with disease.

diverse both at the phylogenetic level and at the functional level [5]. While it is essential to maintain a proper microbial composition to assure efficient wastewater treatment [6,7], the bioengineer has only a limited number of operational handles on the system. The operational variables include aeration, mixing and flow rate, which if not optimally chosen can lead to bioreactor failure [8]. Mathematical models can be valuable tools to assist in the operation and control of these bioreactors, in order to enrich microbial composition in the right type of microbes [9].

Traditional mathematical models of wastewater treatment are based on differential equations that describe microbial population dynamics and the dynamics of chemical compounds in solution or in suspension. Most models adopt variations of the Activated Sludge Model (ASM) [1]. There are presently five versions of the ASM [10] that differ in their level of detail. In general, these models include bioreactions such as degradation of soluble, particulate and colloidal organic carbon sources and of nitrogen (as ammonia, nitrate and nitrite) and phosphorus sources. Microbial processes from mainly three functionally relevant microbial groups mediate these reactions. These microbial groups are ordinary heterotrophic organisms (i.e., organisms that use organic carbon for growth), autotrophic nitrifying organisms (organisms that use inorganic nitrogen sources such as ammonia) and phosphorus accumulating organisms (PAOs; which store phosphorous internally in the form of polyphosphates). This functional grouping was chosen because the goal of wastewater treatment is to remove nutrients before municipal or industrial effluents are released to the environment. In this functional grouping, the microbes do not necessarily belong to the same phylogenetic taxa. An example equation corresponding to PAOs net growth from the ASM2 model is displayed in Fig. 2A.

Even though many engineers rely on ASM to characterize bioreactor properties and designs [11], there is active research to introduce additional levels of detail [12]. Some of the limitations of ASM are due to oversimplified model representation (functional groups) and parameterization [13]. For example, ASM2 was modified to simulate phosphorous removal by PAOs and to include the presence of