Project: The Chemostat and Microbial Communities

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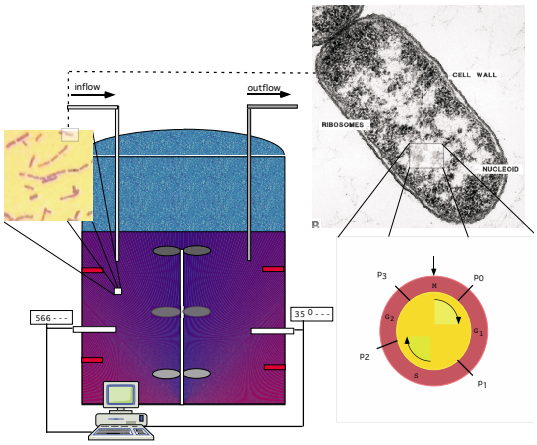
1 Introduction

This project is essentially in population dynamics (Mathematical Biology), but with several interesting real-world applications in mind. In fact, the concept of a bioreactor (chemostat) is essentially the same as saying we study life (microbes or bacteria are the most abundant form of life on the planet) in a well-defined environment, where we have hope to understand the living conditions precisely. Therefore the study of bioreactors, together with new forms of genetic manipulation and even genetic engineering (synthetic biology) provides the most favorable conditions ever to use mathematical modeling to generate a real predictive science in the Life Sciences.



The list of real-world applications is very long:

- Waste water treatment (large tanks with a gigantic microbial community, both in numbers and in numbers of species)
- Biotechnology (industrial tanks used to produce something microbes can synthesize, like biofuel)

- As abstractions of situations found in human bodies, which is interesting for medicine (mostly the gut, intestine)
- As abstractions of real microbial ecosystems in the soil, the sea etc.

2 Mathematical Modelling

As noted in the introduction, bioreactors are ideal objects to advance mathematical modeling in the Life Sciences. Microbes are uni-cellular, and usually very abundant allowing in most generic situations the use of continuum models. Nevertheless each single cell is a highly sophisticated biological object, which allows to study the most essential largely unknown genotype-phenotype relationship, as postulated theoretically by Darwin. In mathematical terms this means we have to study multi-scale systems, we begin typically with cellular biochemistry and genetics, and build up functional models to the level of organelles, and finally whole cell. The interaction of all cells in the bioreactor is then the population dynamics aspect. The latter aspect can be studied either spatially homogeneous, or spatially explicit, leading to either ODE or PDE-type equations. The same is true for all modeling aspects along the genotype-phenotype chain:

- Biochemistry inside the cell can be either spatially explicit (rare) or homogeneously mixed. Using biochemically pathways inside each cell leads to models with high internal structure.
- Cell physiology, like growth, and cell division, can be modeled in different ways.

If we get rid of all sophistication on the cellular level (microbial soup), and assume a homogeneous environment with one so-called limiting nutrient (one concentration of nutrient in the growth medium is determining growth), we get the classical chemostat equations:

$$\begin{aligned} \frac{dS}{dt} &= D(S^0 - S) - \frac{1}{\mu} g(S)x, \\ \frac{dx}{dt} &= (g(S) - D)x, \\ S(0) &= S_0, x(0) = x_0. \end{aligned}$$

Here S is the nutrient concentration, x is the biomass concentration, $D > 0$ is the washout rate, $S^0 > 0$ is the (limiting) nutrient concentration in the feeding bottle, $\mu > 0$ is the growth yield factor, and g(S), the nutrient dependent growth rate, usually modeled by the Michaelis-Menten function, i.e.

$$g(S) = \frac{mS}{k + S},$$

with $m > 0$ the maximal growth rate, and $k > 0$ the half-saturation constant. One can take this simple model, and attach to it more and more structure, like model resolution for individual cells.

2.1 The chemostat story

- The chemostat literature is the most complete mathematical description of any system where population dynamics is considered. See all references (not complete). Perhaps it started with J. Monod, an important French micro-biologist at the Institut Pasteur (see [24]).
- The chemostat story is indeed a story of subsequent generalizations in very many different directions, and therefore can be taken as a paradigm case for mathematical modeling in itself. The chemostat can be extended, as mentioned, to spatial modeling, but it can be also extended to internal structure, i.e. cellular properties, like an explicit modeling of the cell cycle, or biochemical pathways. In addition we can consider periodic in- and outputs for the environment. Or even more complex fluctuations, see also 'batch cultures'.
- Just a view names of important mathematicians associated with the chemostat literature: Paul Waltman, Gail Wolkowiecz, Hal Smith, Betty Tang, Willy Jäger, Odo Diekmann, Horst Thieme, ...

2.2 Batch cultures

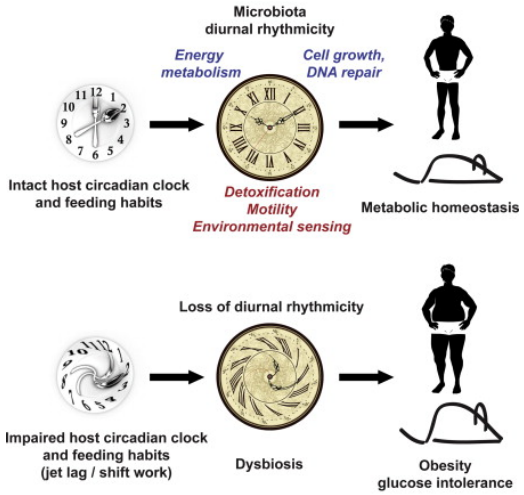
A variant of the chemostat are batch cultures. Here the chemostat is disconnected, and has no exchange with the outside, it is a closed system. In this case we are interested in transients, and a sequence of initial-value problems, which correspond to a repeated set-up of the batch culture. Such arrangements have, for example, been taken in experiments of directed evolution, where the contents of a batch culture is suspended into fresh medium after some time. The new medium can be arranged to imitate certain selective pressures. We will study the situation with evolutionary models of so-called 'adaptive-dynamics' type.

3 An interesting real-world example that could be studied with chemostat theory

Just to motivate you here is the citation of the summary of a recent paper in Cell ([34]):

'All domains of life feature diverse molecular clock machineries that synchronize physiological processes to diurnal environmental fluctuations. However, no mechanisms are

known to cross-regulate prokaryotic and eukaryotic circadian rhythms in multikingdom ecosystems. Here, we show that the intestinal microbiota, in both mice and humans, exhibits diurnal oscillations that are influenced by feeding rhythms, leading to time-specific compositional and functional profiles over the course of a day. Ablation of host molecular clock components or induction of jet lag leads to aberrant microbiota diurnal fluctuations and dysbiosis, driven by impaired feeding rhythmicity. Consequently, jet-lag-induced dysbiosis in both mice and humans promotes glucose intolerance and obesity that are transferrable to germ- free mice upon fecal transplantation. Together, these findings provide evidence of coordinated metaorganism diurnal rhythmicity and offer a microbiome-dependent mechanism for common metabolic disturbances in humans with aberrant circadian rhythms, such as those documented in shift workers and frequent flyers.'



Chemostat theory, with its well-developed approaches to tackle rhythmic driven inputs, could well be used to make a predictive theory out of these findings. And there is indeed a lot of interesting real-world application in this...

4 What to do in this project ?

Depending on the level of the student (Project, MSc, PhD) the student takes one of the following topics:

- A specific application, like biotechnology, waste-water treatment, or the human gut or intestine.

- A specific mathematical challenge, like extension to spatial modeling (PDE) or models with internal structure (Physiologically Structured Population Models, see [23]), or even both.
- An evolutionary setting, for example directed evolution in the context of batch cultures.
- The study of biochemical pathways with the help of the chemostat and bacterial cultures.

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