An Introduction to the Mathematics of Bacterial Growth in the Chemostat Bioreactor

A Foundation Course in Chemostat Modelling

Contents of the Course

Preface

There is a particular pleasure in encountering a mathematical model that is, all at once, physically transparent, analytically tractable, and biologically rich. The chemostat is such a model. It begins with something modest: a pump, a chamber, a bacterial culture, and a nutrient supply. From this it generates a pair of coupled differential equations whose behaviour ranges from complete extinction to stable coexistence, and whose full analysis—from first principles through global stability—can be carried out with nothing more than calculus, linear algebra, and a single conservation argument. That completeness is rare, and it is one of the reasons the chemostat has occupied a central place in mathematical biology for more than seventy years.

There is a further reason, one that goes beyond convenience. The chemostat is not merely a convenient model; it is a genuine piece of the world. Real chemostats exist in laboratories across microbiology, biotechnology, and evolutionary biology. Bacteria really do wash out when the pump runs too fast. Populations really do stabilise at the coexistence equilibrium when the parameters permit it. The mathematics is not a fiction imposed on the biology; it is a language in which something true about life is being said. Learning to read that language carefully—to see why the equations take the form they do, what every term means, why the stability analysis comes out the way it does—is learning something about both mathematics and the living world at the same time.

This course is written for anyone who has met ordinary differential equations and wants to understand, fully and from the ground up, how a mathematical model of bacterial growth is built, analysed, and interpreted. It assumes no prior knowledge of biology beyond the elementary idea that bacteria grow by consuming nutrients, and no prior knowledge of the chemostat. Everything else is developed here. The treatment is careful and unhurried. Derivations are shown in full. Assumptions are named before they are used. Results are interpreted after they are proved. The aim is not to deliver a finished theory but to carry the reader through the making of one.

1. The Historical Origins of Continuous Culture Theory

1.1. Before the Chemostat: Batch Culture and Its Limitations

For most of the history of experimental microbiology, bacterial growth was studied in what is called *batch culture*: a fixed volume of nutrient medium is inoculated with bacteria, the flask is sealed, and the culture is allowed to grow until the nutrients are exhausted. The resulting growth curve—an initial lag phase, an exponential phase, a stationary phase, and finally a decline—became one of the most familiar pictures in all of biology.

Batch culture was enormously productive as an experimental tool, but it carried a structural limitation that became increasingly frustrating as microbiology matured. In a batch culture, conditions change continuously. Nutrients are depleted as bacteria grow; metabolic waste products accumulate; the pH drifts; the composition of the medium at the end of the experiment bears little resemblance to its composition at the beginning. A bacterium growing in the early exponential phase is not growing in the same environment as one growing near stationary phase, even in the same flask. For physiological studies—experiments designed to ask what is happening inside the cell under defined, reproducible conditions—this continuous environmental drift was a serious obstacle. Reproducibility demanded steady conditions, and batch culture could not provide them.

The conceptual solution was to open the flask: to make the culture continuous by supplying fresh medium at a controlled rate and removing spent culture at the same rate, so that the volume of liquid in the chamber remained constant and the system could be driven toward a steady state in which both the bacterial density and the nutrient concentration were time-independent. This idea is so natural in retrospect that it is easy to underestimate the intellectual step it represented. The batch culture paradigm had shaped experimental practice for decades, and the shift to continuous culture was not merely a technical modification; it was a reconception of what the experiments could be.

1.2. Monod and the Kinetics of Growth

The mathematical foundation of the chemostat was laid, in large part, by the French biologist Jacques Monod. In a series of experiments during the 1940s, Monod studied how the growth rate of bacteria depended on the concentration of the limiting nutrient in their environment. He found a relationship that was not linear and not arbitrary: at low nutrient concentrations, the growth rate increased approximately in proportion to the nutrient concentration; at high concentrations, it saturated toward a maximum value that could not be exceeded regardless of how much more nutrient was supplied.

This behaviour was not new to biochemistry. It was exactly the behaviour that Leonor Michaelis and Maud Menten had described in 1913 for the rate of an enzyme-catalysed reaction as a function of substrate concentration. Their analysis—based on the mechanism of reversible enzyme-substrate binding followed by irreversible product release—produced the now-famous Michaelis–Menten equation, in which the reaction rate v at substrate concentration S is

$$v(S) = \frac{v_{\max} S}{K_m + S},$$

where $v_{\max}$ is the maximum reaction rate and K_m is the substrate concentration at which the rate is half its maximum value. Monod recognised that bacterial growth, being ultimately driven by enzymatic reactions inside the cell, should satisfy an analogous relationship, and he proposed the *Monod growth function*

$$\mu(C) = \frac{mC}{a + C},$$

where C is the concentration of the limiting nutrient, $m > 0$ is the maximum per-capita growth rate, and $a > 0$ is the half-saturation constant—the nutrient concentration at which the per-capita growth rate is exactly half its maximum.

It is worth pausing over the qualitative behaviour of this function, because it encodes the biology that drives the entire chemostat model. When C is very small compared with a, the denominator is approximately a and $\mu(C) \approx mC/a$, which increases linearly with nutrient concentration: growth is directly proportional to the nutrient supply and the bacteria are nutrient-limited in the strictest sense. When C is very large compared with a, the denominator is approximately C and $\mu(C) \approx m$, independent of C: growth has saturated and more nutrient cannot accelerate it. The half-saturation constant a governs the transition between these two regimes; a small value of a means the bacterium reaches near-maximum growth at low nutrient concentrations, while a large value means the bacterium is sensitive to depletion even at moderate concentrations.

1.3. The Invention of the Chemostat

In 1950, working independently and publishing within months of each other, two groups arrived at the continuous culture device that would become known as the chemostat. Jacques Monod, at the Institut Pasteur in Paris, described what he called the *bactogène* in a paper that connected his growth kinetics directly to the steady-state behaviour of a flow-through culture. Almost simultaneously, Aaron Novick and Leo Szilard at the University of Chicago published their own device, which they named the *chemostat*—a contraction of *chemical environment is static*—and it is this name that has persisted.

The key insight shared by both groups was that in a flow-through culture operating at steady state, the growth rate of the bacteria is not a free variable determined by the biology alone; it is controlled by the operator through the flow rate. At steady state, bacteria can neither accumulate nor decline: they must be growing at exactly the rate at which the flow is removing them. Since the removal rate is determined by the dilution rate $D = r/V$—the ratio of volumetric flow rate to chamber volume—the steady-state bacterial growth rate is pinned to D, and the operator therefore controls the growth rate of the bacteria by controlling the pump. This was a conceptual and experimental revelation: for the first time, it was possible to maintain bacteria indefinitely at a prescribed, constant growth rate under stable environmental conditions.

The mathematical theory of the chemostat developed in tandem with the experimental practice. By the 1970s, the model analysed in this course had been studied rigorously by several groups, and its complete stability theory—including the global results that are among its most important features—was established. The chemostat became a standard object of study in mathematical biology and ecology, appearing as a prototype for resource-consumer models and as a testing ground for techniques in nonlinear dynamical systems. Its influence extends to epidemic modelling, population dynamics, and evolutionary theory, because the structural features of the model—a growth process competing against a removal process, with a threshold parameter determining which wins—recur across all of these fields.

2. The Physical Setup and the Meaning of the Variables

2.1. The Chemostat as a Physical Device

A chemostat consists of a cylindrical growth chamber of fixed volume V, measured in litres. Fresh nutrient medium is pumped continuously into the chamber at a fixed volumetric flow rate r, measured in litres per hour: this is simply the volume of liquid entering the chamber per unit time. Simultaneously, culture is withdrawn from the chamber at the same rate r, so the total volume of liquid inside the chamber remains constant at V for all time. The incoming medium is sterile—it contains nutrients but no bacteria—and is maintained at a fixed nutrient concentration C_0, measured in grams per litre (g/L). The bacteria inside the chamber consume the nutrient as they grow, and both bacteria and residual nutrient are carried out continuously in the exiting flow.

The single most important derived quantity describing the operation of the chemostat is the *dilution rate* $D = \frac{r}{V}$, measured in hours^{-1}. Its value is the fraction of the chamber

contents replaced per unit time: if $D = 0.5\ \mathrm{h}^{-1}$, then half the chamber volume is exchanged every hour. Its reciprocal, $1/D$, is the mean residence time of a fluid particle inside the chamber—the average time a molecule of liquid spends in the chamber before being carried out. The dilution rate is the operator's primary control variable: it is set by adjusting the pump, and every qualitative feature of the chemostat's long-term behaviour depends critically on its value relative to the biological parameters of the bacterial culture.

2.2. Concentrations, Densities, and Total Masses

The two state variables of the chemostat model are the nutrient concentration $C(t)$ and the bacterial density $B(t)$, both measured in grams per litre (g/L) and both functions of time t.

It is essential to understand precisely what these quantities represent. The nutrient concentration $C(t)$ is the mass of nutrient per unit volume of chamber liquid at time t: it is a density, telling you how much nutrient is packed into each litre, not how much nutrient exists in total in the chamber. The total mass of nutrient inside the chamber at time t is the product of this density and the chamber volume,

$$\text{total nutrient mass} = V \cdot C(t) \quad [\mathrm{g}].$$

Similarly, $B(t)$ is the bacterial mass per unit volume of chamber liquid, and the total bacterial mass inside the chamber is $V \cdot B(t)$.

This distinction—between a concentration as a density and a total mass as the product of that density and volume—is not a technicality. It is the reason the derivation of the model equations begins by writing balance equations for total masses $V \cdot C(t)$ and $V \cdot B(t)$, rather than for the concentrations directly. The physical processes of inflow and outflow are naturally expressed as rates of change of total mass—because it is mass that flows through the pump, not concentration—and writing the balances in terms of total mass allows each process to be stated as an unambiguous flux. Once the balance is established, division by the constant V yields the equation for the concentration itself.

2.3. The Monod Growth Function in the Model

The per-capita growth rate of bacteria in the chemostat is governed by the Monod function introduced in Section 1. In the notation of the model,

$$\mu(C) = \frac{mC}{a + C},$$

where $m > 0$ is the maximum per-capita growth rate (h^{-1}) and $a > 0$ is the half-saturation constant (g/L). For a bacterial density $B(t)$, the total rate at which bacterial mass is

produced per unit volume of chamber liquid is $B(t) \cdot \mu(C(t))$, and over the full chamber volume V the total bacterial production rate is $V \cdot B(t) \cdot \mu(C(t))$ grams of bacteria per hour.

Bacterial growth consumes nutrient, and the rate of nutrient consumption is related to the rate of bacterial production through the *yield constant* γ, defined as

$$\gamma = \frac{\text{bacterial mass produced}}{\text{nutrient mass consumed}} \quad \left[\frac{\text{g bacteria}}{\text{g nutrient}}\right].$$

By definition, producing one gram of bacteria requires $1/\gamma$ grams of nutrient. Producing bacteria at the total rate $V \cdot B(t) \cdot \mu(C(t))$ therefore requires nutrient at the rate

$$\frac{V \cdot B(t)}{\gamma} \cdot \frac{mC(t)}{a + C(t)} \quad \text{[g nutrient/h]}.$$

The yield constant γ is a fixed biological property of the bacterium-nutrient pair, measuring how efficiently the bacterium converts food into biomass. It appears in the model only in the nutrient equation—only in the term that asks how quickly the food supply is being consumed—and is entirely absent from the bacterial equation, which asks only how quickly the bacteria themselves are multiplying.

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