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Intermediate Asymptotics

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When I entered my third year of university study, I was introduced to the topic of Fluid Mechanics – the mathematical analysis of the flow of liquids and gases. I found that the concept of a fluid that is analyzed in *that* context is not exactly that which applies to real fluids. The "fluids" discussed in the lectures had local properties, such as density, pressure and velocity, described by continuous functions for which it was possible to assign values at points situated in the fluid. However, we all know that real fluids are composed of atoms and/or molecules and so do not correspond to such a description. This discrepancy is addressed in the opening chapter of one of the textbooks we were set: D. E. Rutherford's[2] *Fluid Dynamics* (Edinburgh: Oliver & Boyd, 1959). Rutherford's careful discussion bears quoting in full.

> A portion of a real fluid is composed of a very large number of molecules each of which has its own mass and velocity. At any instant the several molecules within a given closed surface have a great variety of velocities, since the velocities vary both in magnitude and direction from molecule to molecule. If the closed surface has a small but finite volume V it is possible to consider the average mass per unit volume and the average vector velocity within the surface. These quantities might be regarded as the density ρ and the velocity $\mathbf{q}$ of the fluid at some point within V, though it must be remembered that their values depend upon the size of the small volume considered. In fact, if the volume be too small it may contain only one, or two, particles or even none at all, and the quantities then evaluated could hardly be regarded as the density and velocity of the fluid. On the other hand, if the volume chosen be too large ρ and $\mathbf{q}$ can only be regarded as average values and will not give a meaning to density or velocity at a point in the fluid.
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> The truth of the matter is that the concepts of density and velocity at a point in the fluid pertain only to the idealised notion of a continuous fluid and are not strictly applicable to a real fluid. The mathematical difficulties indicated above arise from the fact that a real fluid is a discrete assemblage of molecules and is not a continuous fluid.

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[2]This is not Ernest Rutherford, the Nobel Prize winner, but another person with the same surname.

Perhaps it needs to be said here, in the light of the disclaimers that Rutherford advances, that the science of Fluid Mechanics nevertheless provides excellent descriptions, and indeed predictions, of the behavior of real fluids. The treating of a real fluid as a continuum is only an approximation, but nonetheless a very good approximation.

When Rutherford carefully chose the volume V to be neither too large nor too small, he was embarking upon what another mathematician, Grigory Barenblatt, was to call "intermediate asymptotics". The word "asymptotics" in this context may be taken to mean "approximations"; it relates to the word "asymptote", with which readers will be familiar, but extends the meaning beyond that more usual sense of the word. By "intermediate", Barenblatt signified that it was to be understood as applying away from extreme situations. In the case just cited, the volume V is to be *intermediate* in size between being too large or too small; these extremes are to be avoided.

Here is what Barenblatt has to say (in his book *Scaling, Self-Similarity and Intermediate Asymptotics* [Cambridge University Press, 1996]): "[*Intermediate asymptotics* are] asymptotics valid for times and distances at which the influence of fine details of initial and/or boundary conditions is lost although the system is still far from an ultimate equilibrium."

In another of his books, *Dimensional Analysis* (London: Gordon & Breach, 1987), he supplies an interesting visual example. A picture composed of 560 (28×20) monochromatic squares is displayed. If we view this from a distance neither too near nor too far, we readily recognize it as the *Mona Lisa*.

In one of my own researches, I needed to use intermediate asymptotics. With a student and a colleague, I was looking into the so-called Michaelis-Menten[3] reaction, which treats the action of enzymes on biochemical substrates. I had been introduced to this material when I studied Biochemistry back in my student days, and had had my interest aroused by my dissatisfaction with the approach outlined in the textbooks of the time. Indeed, my doubts were shared by others; one group of researchers said that one of the hypotheses there entertained, if treated correctly, led to a differential equation "no biochemist has encountered or would wish to". Thus my interest in the topic.

Michaelis and Menten envisaged that an *enzyme* (a catalytic protein) E would react with another chemical species (the *substrate* S) by first binding to it to form a *complex* C which, in its turn, could either break apart again to restore the original chemicals, or else go on to form a new pair of chemical species: the original enzyme E and a *product* P. Schematically this is represented symbolically as:

$$E + S \rightleftarrows C \to E + P.$$

Chemists represent the concentrations of the different chemical compounds by enclosing the relevant symbols in square brackets; thus $[E]$ stands for the concentration

[3]Leonor Michaelis (1875-1949) was a German-born biochemist. He fell out with the German academic establishment when he suggested (correctly) that a widely used pregnancy test was unreliable. He left Germany and ultimately settled in the USA. Maud Menten (1879-1960) was a Canadian medical scientist. As a woman, she was denied the prospect of a research career in her native country and so travelled abroad in 1912; in 1916 she obtained her doctorate under Michaelis's supervision. She later worked in both the USA and Canada after entrenched attitudes had softened.

of enzyme, etc. We represent time by t and imagine that when $t = 0$, we start the reaction by mixing pure enzyme with pure substrate, that is, at that point in time, $[E] = E_0$, $[S] = S_0$ (say) and $[C] = [P] = 0$.

The subsequent values of these quantities are determined from a chemical law known as the "Law of Mass Action", which describes their rates of change. The three different reactions (indicated by the three arrows in the display above) are each characterized by specific constants, known as "rate constants". The first reaction (the combination of *E* and *S* to form *C*) is given a rate constant k_1; the reverse reaction (decomposition of *C* to re-establish *E* and *S*) has a constant k_{-1}, and the final reaction's rate constant is called k_2. The rate equations then read:

$$\begin{aligned}
\frac{d}{dt}[E] &= -k_1[E][S] + (k_{-1}+k_2)[C] \\
\frac{d}{dt}[S] &= -k_1[E][S] + k_{-1}[C] \\
\frac{d}{dt}[C] &= k_1[E][S] - (k_{-1}+k_2)[C] \\
\frac{d}{dt}[P] &= k_2[C].
\end{aligned}$$

Besides these four differential equations, there are two *conservation equations*, expressing the fact that the total concentration of enzyme (whether complexed or not) must be the same at all times, and the total concentration of substrate (whether complexed, converted to product or else still around as substrate) must also remain the same. So we have:

$$[E] + [C] = E_0$$

$$[S] + [C] + [P] = S_0.$$

These two equations allow us to reduce the system of four differential equations to a simpler system involving only two. This pair of equations can be written in many ways, but the one below is especially convenient.

$$\frac{d}{dt}[S] = -k_1(E_0-[C])[S] + k_{-1}[C]$$

$$\frac{d}{dt}[C] = k_1(E_0-[C])[S] - (k_{-1}+k_2)[C].$$

Indeed, further simplification is possible. As the reaction proceeds, [*S*] is progressively reduced from S_0 to zero while [*C*] begins at a value 0, then increases to higher values, before (eventually) returning to its initial (zero) value.

We can write:

$$[S] = yS_0 \quad \text{and} \quad [C] = zE_0 \qquad (\text{where} \quad 0 \le y \le 1, 0 \le z \le 1),$$

and define

$$\tau = k_1 E_0 t,\ \mu = E_0/S_0, \nu = k_2/(k_1 S_0), \eta = k_{-1}/(k_1 S_0)$$

so that after some simpliflication we reach a standard form:

$$\frac{dy}{d\tau} = -y + (y + \eta)\, z$$
$$\mu \frac{dz}{d\tau} = y - (y + \nu + \eta)\, z.$$

(I leave the reader to verify this.) These equations are an exact translation of the Michaelis-Menten reaction scheme into mathematical language. However, no exact mathematical solution (even after all this simplification) can be provided. We are forced back onto approximations, and this is where the intermediate asymptotics come in.

At the outset, we mix an amount E_0 of enzyme with an amount S_0 of substrate, and in the practical (biological) situation, S_0 is a lot larger than E_0. In other words, μ is very small. The temptation is to approximate by setting $\mu = 0$. However, if we then set $t = 0$, $y = 1$, $z = 0$, the equation makes nonsense. This set of values is precisely the set that applies initially, so that the approximation envisaged is invalid for small values of t. We need to restrict ourselves to larger values of t, and this is what Barenblatt meant by "times ... at which the influence of fine details of initial ... conditions is lost". When t is very small, the value of $\frac{dz}{d\tau}$ has to be very large to make the product on the left-hand side of the second equation equal to the moderate value on the right. We cannot use the projected approximation for small times.[4]

Nor can we use this idea for very large times. When the reaction is nearing completion, we are approaching the state of equilibrium. When equilibrium is reached, [S] = 0 and [E] = E_0. All the substrate has been converted to product, the enzyme is restored to its original state, and there is no more complex left: [C] = 0 and [P] = S_0. The analysis of this aspect of the reaction needs a somewhat different form of the basic equations, and will not be pursued here. However, this is what Barenblatt is talking about when he writes about "the system [being] still far from an ultimate equilibrium."

So let us now look at the intermediate stage. Here we *can* apply the approximation $\mu = 0$, and moreover, although initially $\frac{dz}{d\tau}$ is large (as we have seen) and although ulttimately it is large negative (which I haven't proved here), the system must pass through a stage for which it is zero and around which it is very small. In analyzing this stage of the reaction, we are therefore led (on two grounds) to neglect the term $\mu\frac{dz}{d\tau}$ in the second of the basic equations and so set $y = (y + \nu + \eta)\, z$. From this and the first of the basic equations, we may now deduce $\frac{dy}{d\tau} = -\frac{\nu y}{y+\nu+\eta}$ (Again I leave it to the reader to fill in the details.)

[4]This type of problem was discussed in more detail in my *Function* column of February 2004.

Now we are in a position to construct, using *sound* mathematics, the law that Michaelis and Menten announced and which, for a long while was justified by demonstrably *unsound* arguments. If we take this last equation and express it in terms of the original notation, we reach (and yet again I ask readers to fill in the details):

$$\frac{d[S]}{dt} = -k_2 E_0 \, [S] \, / \left\{ [S] + \frac{k_{-1}+k_2}{k_1} \right\}$$

Now biochemists are especially interested in the rate at which the product appears; this is termed the *velocity* of the reaction. Here the velocity, V, is given by

$$V = \frac{d}{dt} \{[P]\} = \frac{d}{dt} \{S_0 - [S] - [C]\} = -\frac{d}{dt}[S] - \frac{d}{dt}[C] \approx -\frac{d}{dt}[S],$$

This last approximation follows because $\frac{d}{dt}[C]$ is proportional to $\frac{dz}{d\tau}$ which we have seen to be small during the intermediate stage. So, putting all this together, we have

$$V \approx \frac{k_2 E_0 [S]}{[S]+K_m} \text{ where } K_m = \frac{k_{-1}+k_2}{k_1}$$

The constant K_m is known as the "Michaelis Constant", and the suffix m is there to remind us of this name. Biochemists also alter the notation somewhat. Again I leave some details to the reader, but it is not hard to show that, when we plot V against $[S]$, the result is a steadily climbing curve that ceilings out ("asymptotes" in the more familiar sense) to the value $k_2 E_0$, which, because it is an upper bound on V, is termed $V_{\max}$. We thus have as the statement of the Michaelis-Menten Law as usually given:

$$V = V_{\max} \frac{[S]}{[S]+K_m}$$

This derivation is legitimate, just as long as we remember that it has its limitations: it does not apply to the very early stages of the reaction nor to the vary last.

I came across another take on intermediate asymptotics recently. Michael Shermer, who writes the *Skeptic* column for *Scientific American*, devoted his September and October 2008 articles to what the popular author Richard Dawkins calls "Middle World", or in Shermer's terminology "Middle Land". Shermer writes:

> In the Middle Land of space, our senses evolved for perceiving objects of middling size—between, say, grains of sand and mountain ranges. We are not equipped to perceive atoms and germs, on one end of the scale, or galaxies and expanding universes, on the other end. In the Middle Land of speed, we can detect objects moving at a walking or running pace, but the glacially slow movement of continents (and glaciers) and the mind-bogglingly fast speed of light are imperceptible. Our Middle Land timescales range from the psychological 'now' [approximately] three seconds in duration ... to the few decades of a human lifetime, far too short to witness evolution, continental drift or long-term environmental changes.

Shermer, of course, is concerned to discuss the limits that our Middle Land experience imposes on our modes of thought. We find the laws of relativity (which involve the velocity of light) and those of Quantum Physics (which treat the very small) hard to grasp because they lie outside our Middle Land comfort zone. Barenblatt, by contrast, shows the benefits of life in Middle Land—benefits that persist as long as we remain aware of the limitations involved.

Further Reading

The Michaelis-Menten reaction is the subject now of a vast literature, of extremely varying quality. This is true of what is available on the web as well as to the printed accounts. The first accurate treatment is that of Heineken, Tsuchiya and Aris in the very first issue of the journal *Mathematical Biosciences* (1967). This study already goes way beyond the brief synopsis given here, and in particular, discusses approximations valid in the early stages of the reaction and how they may be adjoined to those valid in the intermediate stages. My co-workers and I wrote in 1981, and extended the discussion to the late stage, when equilibrium is close to being achieved. Since then, there has been more progress. In particular the extensive writings of the late Lee Segel have added yet another chapter to the story.

Yet other lines of research have considered modifications to the basic model. One such amendment deserves special mention. The basic reaction scheme envisaged by Michaelis and Menten was:

$$E + S \rightleftarrows C \rightarrow E + P.$$

Later researchers have thought that this requires elaboration. In its place, they treat the more complicated process

$$E + S \rightleftarrows C_1 \rightleftarrows C_2 \rightarrow E + P.$$

Here the complex is envisaged as existing in two possible forms, one of which can revert to its original state, but the other of which can produce (irreversibly) product in place of substrate. This elaboration has a lot of chemical plausibility, and leads to more complicated mathematics. However, the success of the simpler model means that many of these additional complications turn out not to be particularly important in the analysis of the real-life biochemical interaction.