The Difficulties of Mathematising Biology

(A Minority Report)

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Plan

- An exhortation
- An example from Physics
- Mathematics in Biology: two examples of articulation models
- A quotation from Wittgenstein

Dedicated to the memory of Lee Aaron Segel (1932-2005)

C. S. Peirce (1839–1914): The "highest maxim of logic" is

Do not block the way of inquiry

- By making absolute assertions submitted as absolute truths;
- By claiming that something transcends human knowledge and thus cannot be known;
- By stating that a proposition is basic or unexplainable;
- By claiming that some law or truth has found its last and perfect formulation.

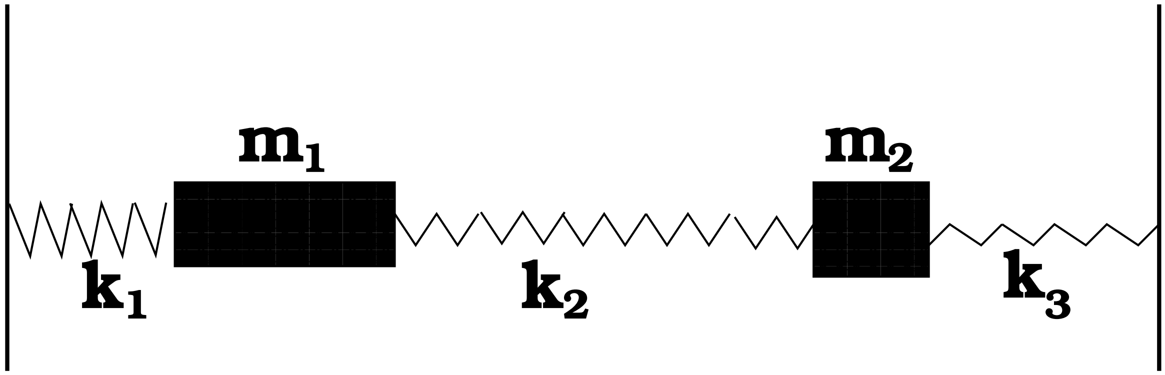
What does it mean to mathematise an area?

In brief, in a mathematised area we accept mathematical *arguments* as *explanations*. The locus classicus is physics:

Consider a system of 3 springs and 2 weights (no gravity effects, no air resistance, which is surprisingly easy to arrange). Make the following assumptions:

1. The weights are point masses (m_1 and m_2);

2. The springs are Hookean.

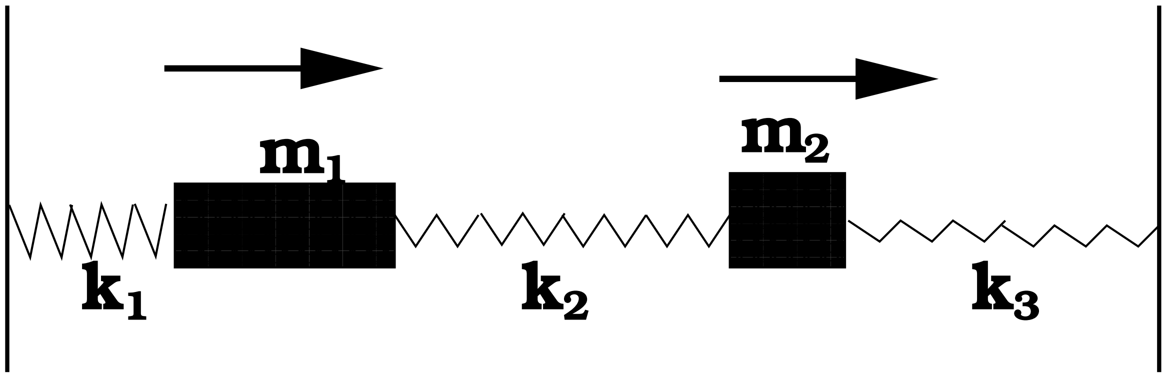


Now use a piece of magic:

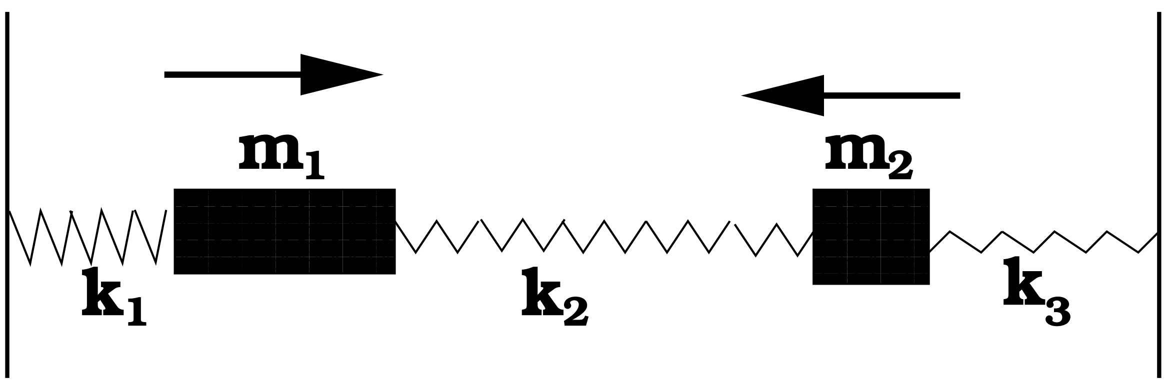
Newton's second law!

... and you get a system of two coupled second order ODEs in variables $x_1(t)$ and $x_2(t)$, the distances of the centres of mass of the two weights from, say, the left-hand wall.

Now, usually, the motion is not periodic, but one can compute initial conditions such that it is; in fact there are two different types of periodic motion:



In−phase motion



Out−of−phase motion

These have periods T_i and T_o, respectively, and it is amazing, having computed their values theoretically, i.e. from the elasticity matrix of the ODE model, to see experimentally (in a system in which the masses are lumps of matter of length circa 10–15cm, the springs are real coils of steel, there is gravity and air resistance) agreement up to a tenth of a second.

So far so well modelled. . . But there is more: in every system one plays with, $T_i > T_o$.

Why is that?

I can see no other (rigorous) answer **but**: if you consider the elasticity matrix, work out its eigenvalues and from them the periods, **this is what you get.** Unlike Descartes (for example) and like Newton, we accept this as an **explanation**.

Let us go through the main ingredients of what gives us the confidence to accept a mathematical answer to a **why** question:

1. The fact that our magic natural law admits of a mathematical statement;

2. The fact that our model is insured against refinement: every refinement is a **regular perturbation** of the model.

Regular vs. Singular

Suppose we have a "model" for a phenomenon involving a variable y. Suppose the modelling process leads us to an equation of the form

$$a_1 y - a_0 = 0,\ a_1 \neq 0.$$

Then if any refinement of this model just introduces small changes into a_1 and a_0, we are OK: these perturbations are **regular**.

But suppose the more refined model is

$$a_2 y^2 + a_1 y - a_0 = 0.$$

The set of solutions for $a_2 = 0$ is nothing like the set of solutions for a_2 as small as the size of one over the mass of the universe (in pounds): this perturbation is **singular**.

Singular perturbations occur very often when you make a guess about the dimensionality of your problem and have to revise it upwards later.

[Sometime you can get away with this; say, in neglecting inertial terms in wave equations. But in each such case there is a theorem to be proved.]

Now back to our points 1. and 2.: these exemplify E. Wigner's **Unreasonable Efficacy of Mathematics**. . .

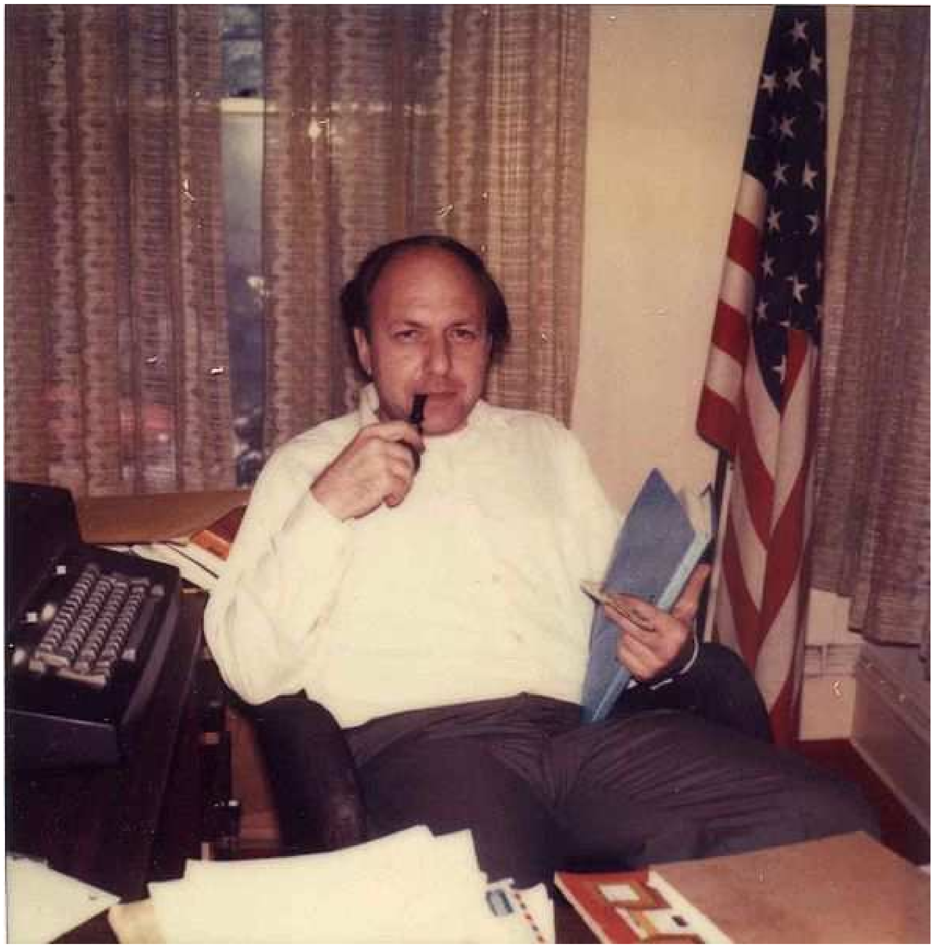
[in Physics; on which V. I. Arnol'd remarked that "a corollary to it is the Reasonable Inefficacy of Mathematics in Biology and Economics."]

To summarise: it is not clear to me how you can mathematise an area that a) has no mathematically expressed laws and b) in which you cannot be assured that model refinement is a regular perturbation.

[Of course in biology we accept the laws of mass-action kinetics. Seems to me that these are sometimes wrong (ecology) and sometimes simply not enough (see below).]

Note that a) and b) are fundamentally different. One seems to me an ontological statement and the other, an epistemological one.

Perhaps we will get somewhere with a) if we listen more carefully to R. Rosen (1934-1998). . .



. . . so that we have something to add to:

> "Biological systems are high-dimensional, tightly coupled, stochastic dynamical systems."

Hmmm. They are also alive, non?

There are two further puzzles, the puzzle of **constants** and the puzzle of **complexity**.

Concerning the first of these: note that both Newton's second law and Hooke's law are assumptions, but these are different. If Hooke's law does not hold, spring constants, which we find by spring extension experiments, do not *mean* anything.

Frequently, models in biology have the following fundamental structure: We have a puzzling phenomenon P. Assumptions A lead to consequences C that can be interpreted as being 'similar to' to P. Therefore if assumptions A hold, P stops being surprising.

I.e. Peircian abduction and in no way a justification of assumptions A.

$\ldots$ Also note that A embody our understanding. So it is not clear how using a model, the assumptions of which are at play themselves, can positively and unconditionally further our understanding. Think about the $T_o < T_i$ question if we are not sure of Newton's second law. Now puzzle out how to model "complex systems".

And now the constructive bit

Even though I do not think that “biology is the new physics” (and neither is economics), I think mathematics has a lot to contribute to biology.

Mathematics is: a way of thinking, a compendium of results on entities involving numbers or having spatiotemporal extension, a treasury of concepts.

Hence it can serve as

- a source of articulation models;
- a “logic inspector”.

(But *prends garde à la douceur des choses*: remember catastrophe theory, fractals, deterministic chaos.)

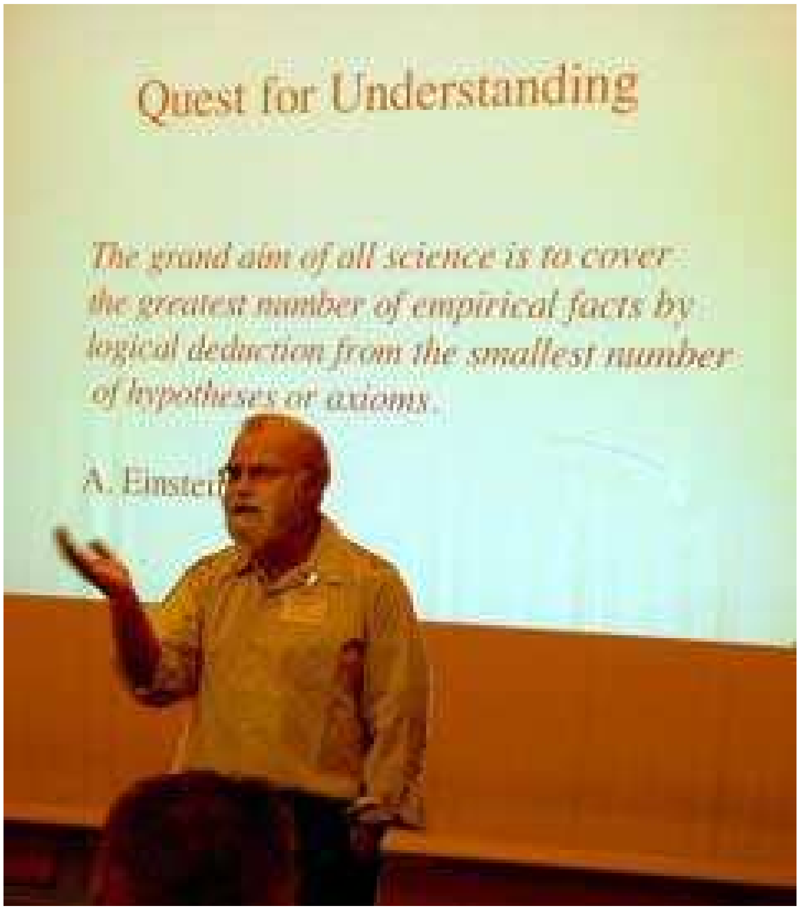
[Note that logical inference, which is what models promise, is a very specific type of a causal relation. The right framework in which to discuss how it interfaces with the natural world is Rosen’s Modelling Relation.]

Articulation Models

An articulation model of a "system" S is another "system" M, consideration of which allows us to further a study of S (think about S, understand it better, find new ways of prodding it, connect S to some other "system" S', etc.).

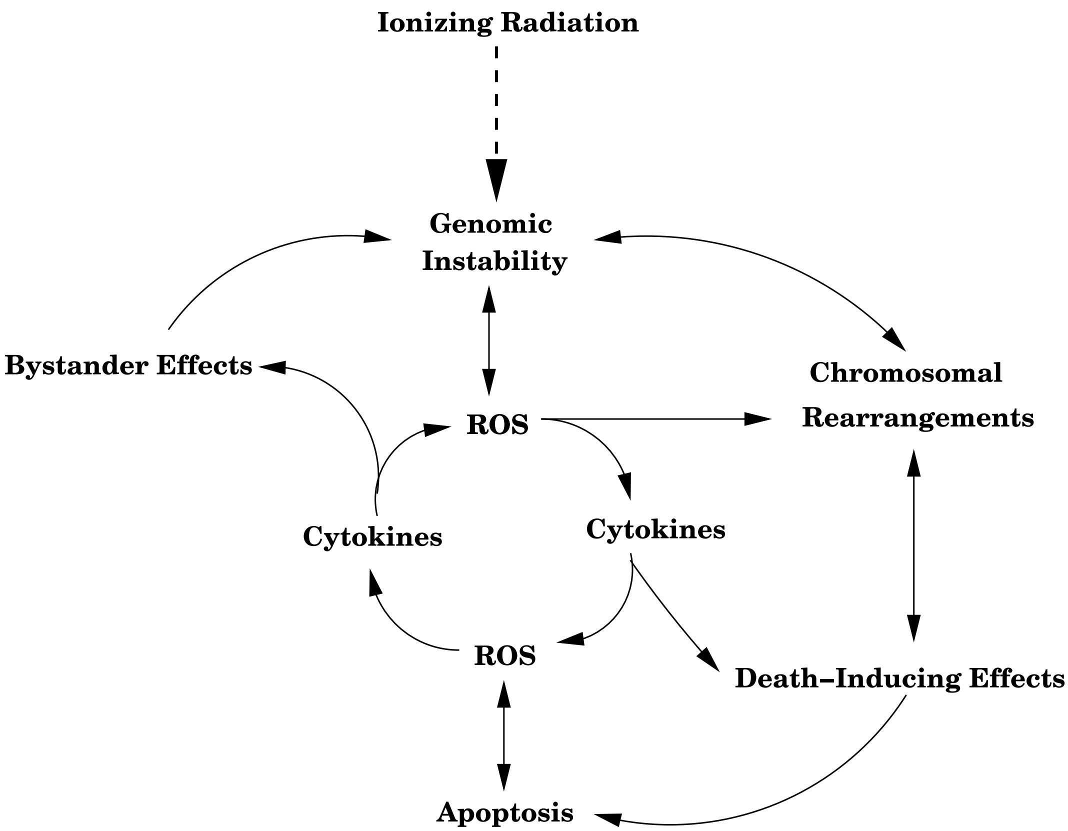
The concept is due to the theologian Ian T. Ramsey (see *Models and Mystery*, OUP 1964). A somewhat playful example of Ramsey is this: "A master of a college is like a figurehead on a ship." Try this for yourself.

A personal remark



The work of Lee Segel, from the Keller-Segel model of chemotaxis to his later work on distributed control in the immune system, exemplifies (though I am not sure he would have agreed) a move from modelling what are in essence mechanical systems to suggesting articulation models with very simple mathematics that mainly serves to emphasise plausibility.

Some Biology



This is W. F. Morgan’s scheme of non-targeted radiation effects (Oncogene **22** (2003), 7094-7099).

His description of the relation between ROS and Cytokines is in terms of a **vicious cycle**. [Vicious cycles are abundant in mechanistic explanations of disease; see M. Pall’s work on CFS, fibromyalgia etc.]

This is unproductive on many levels. For example, because it leads us to envisage a dynamic process. A much better articulation model comes from realising that

Vicious cycle = Bistability

Once you have this idea, which is in its nature mathematical, a whole research programme opens up. Concepts such as hysteresis, saddle-node bifurcations, catastrophes (!) can be brought to bear on understanding; questions about minimal topologies **and biological functions** that give rise to bistability can be asked; one can think about negative feedbacks that would render the system monostable, rôle of hub proteins such as p53, and so on.

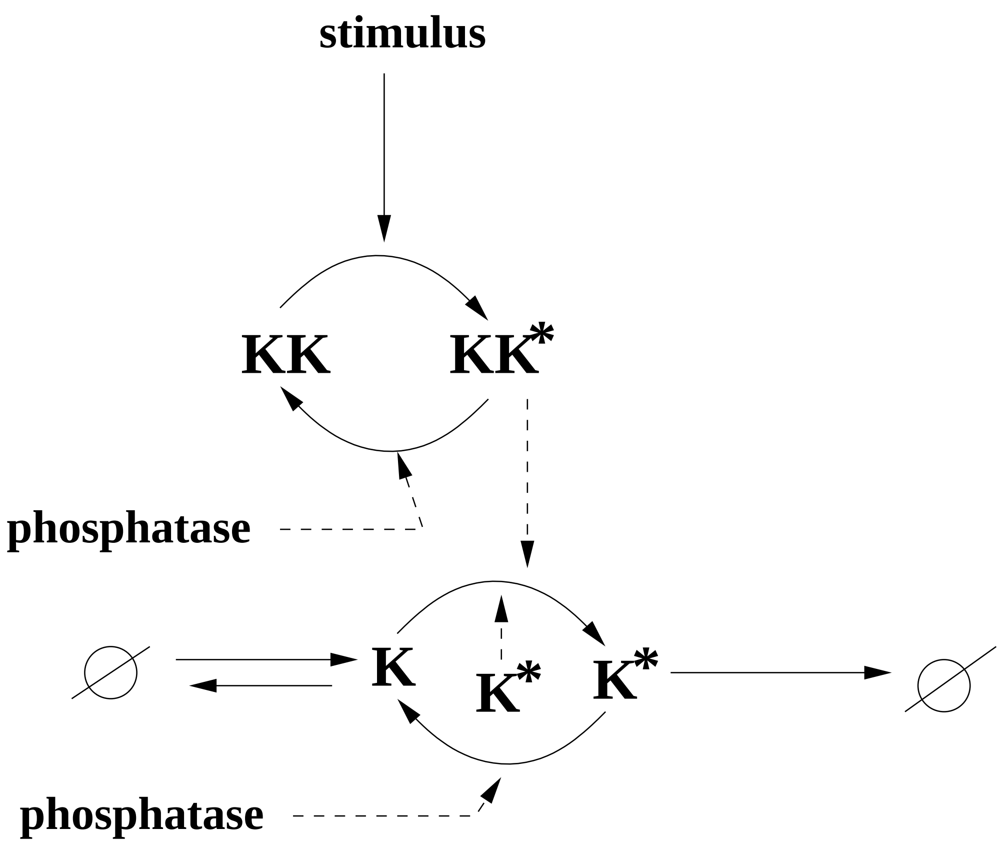
Perhaps some of the work done on mathematical modelling of bistable systems might be useful. . .

. . . Not really. Most theoretical work is of the following form: if network topology is such and such, the system is monostable. It does not give guidance how to explore parameter space for bistability. Much work that actually shows bistability works with models that are simply wrong.

Logic Inspection

Many natural scientists make plausible claims that are mathematical in nature; what (only) mathematicians can do is to prove or disprove them.

Here is an example (MG and S. D. Webb (2009)). In a paper in PNAS **82** (1985), pp. 3055–3057, J. Lisman suggested an autophosphorylating kinase memory switch that works as follows:



The kinetic equations are:

$$\begin{aligned}
\frac{dK}{dt} &= \alpha - dK - f_1 K K^* + b_1 C_{\mathrm{K}} + f_4 C_{\mathrm{P}}, \\
\frac{dK^*}{dt} &= \; - d^* K^* - f_1 K K^* + b_1 C_{\mathrm{K}} + 2 f_2 C_{\mathrm{K}} \\
&\qquad\qquad - f_3 K^* (P_{tot} - C_{\mathrm{P}}) + b_3 C_{\mathrm{P}}, \\
\frac{dC_{\mathrm{P}}}{dt} &= f_3 K^* (P_{tot} - C_{\mathrm{P}}) - (b_3 + f_4) C_{\mathrm{P}}, \\
\frac{dC_{\mathrm{K}}}{dt} &= f_1 K K^* - (b_1 + f_2) C_{\mathrm{K}}.
\end{aligned}$$

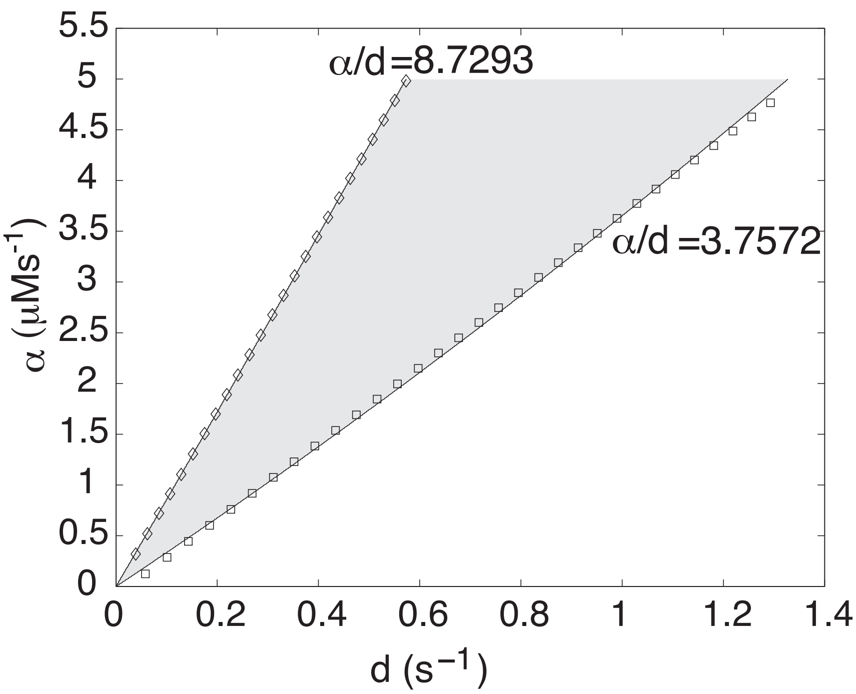
The terms in red are protein turnover parameters, if α and d, d^* are zero, there is no protein turnover.

Lisman is right in that if the red terms are zero, it is easy to find conditions under which there is bistability. But he also claims that these conditions are insensitive to the red terms if they are small enough:

> "A switch of this kind is a dynamic switch and will therefore not be reset by reasonable levels of protein turnover."

This is incorrect, and Lee Segel would have spotted it without any analysis: it is the ratio α/d that has the dimensions of concentration, and this can be large if both α and d are as small as you wish.

In fact, putting for simplicity $d = d^*$, for reasonable values of all the kinetic parameters, one can work out the region in (d, α) plane in which one has bistability. It is a wedge, so the model is not **structurally stable** (and neither are many other bistability models). This immediately raises questions (which means that…).



So: Even by simply providing fruitful articulation models and enforcing a higher level of rigour in mechanistic thinking mathematics is a knowledge discovery tool in biology.

A final thought: The mathematisation of physics necessitated the development of mathematics needed for physics. Look at 18th-19th century mathematicians (Laplace, d'Alembert, Fourier). How and why can one expect to mathematise biology with that toolkit? What new mathematics is needed? Category theory á la Ronald Brown's work could be a good place to look.

The quotation from Wittgenstein

> In the course of a scientific investigation we say all kinds of things, we make utterances whose role in the investigation we do not understand. For it isn't as though everything we say has a conscious purpose; our tongues just keep going. Our thoughts run in established routines, we pass automatically from one thought to another according to the techniques we have learned. And now comes the time for us to survey what we have said. We have made a whole lot of movements that do not further our purpose, or that even impede it, and now we have to clarify our thought processes philosophically.

(1947; *Culture and Value*, p. 65)