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# PHYSIOLOGICAL CONTROL— A PHYSICAL VIEW: LIFE AND THE BIOCHEMICAL OSCILLATOR

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The author's experience originated in instrumentation, automatic regulation, and control. There is a little known background in these fields of interest to the subject of the chemical oscillator. In the 1930's, Mason was involved in how to regulate and control refineries and, of necessity, began to innovate. Building on those applications, as research director for The Foxboro Company he developed the first line of pneumatic automatic controllers for process industry variables. He was an inventive genius, seminal in developing a theoretical and practical background for many major creators in control.

In the late 1940's, Mason helped to bring the subject of automatic control into maturity through the precursor of the present Gordon Research Conferences. There, as du Pont's consultant in automatic control, and in the Instruments and Regulators Division of the American Society of Mechanical Engineers, he spread the gospel of dynamic analysis and automatic control to the chemical process industries and to their outstanding practitioners. Mason's control point of view was influenced by the predominant R-C character of chemical process systems. First-order relaxational kinetics, holdup times, fluid and thermal resistances, and capacitances were the components and items that he saw. Controllability was largely influenced by these characteristics. Difficulties were encountered with interacting rather than noninteracting systems, with high-order systems, with the concept of controllability, and with the methods of relating the system's characteristics to setting the constants of three-mode controllers.

In the 1950's the author outlined a general distributed R-C analysis of the problem of controllability for Mason in an attempt to clarify the problem. By then, the chemical engineers of the process industries were ready for automatic control of both batch and continuous processes, and, in fact, for computer control. Dynamics beyond the characteristics of R-C networks were gradually encountered, and the subject of chemical oscillations appeared on the more immediate agenda of history, particularly with fast catalytic processes and batch polymerization.

For example, in the author's experience at about that time (1960), some cooperative study with a chemical engineering group, under Seymour Calvert at Case, raised the question of R-C-L dynamics in various batch and continuous chemical processes. In the author's group, a peculiar dialogue took place. It appeared that the physicist took for granted that the chemist had the capability for providing chemical oscillators as part of his repertoire. Both were shocked when the physicist realized that the chemist did not have this, that all of the chemist's processes were degradative relaxations, and the chemist was shocked to find that the physicist didn't realize this. At that time the dialogue was resolved by suggesting that if a chemical reaction were coupled to another system, such as a mechanical system with inertia, this could resolve the question, and chemical oscillators could be built. After all, the point was made that all the practical chemical thermodynamic engines worked this way, and coupling was the essential process (in a mathematical sense) by which basic first-order processes were connected together. The detail of producing 180 deg. phase shift, leading for example to

$$m\ddot{x} + kx = 0$$

in a mechanical system, instead of leading to a negative sign, as in a chemical system

$$\dot{x}_1 + k_1 x_2 = 0 \quad \text{and} \quad \dot{x}_2 + k_2 x_1 = 0$$

so that

$$\ddot{x}_1 - (k_1 k_2) x_1 = 0 \quad \text{and} \quad \ddot{x}_2 - (k_1 k_2) x_2 = 0$$

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appeared to be only a minor issue contained in finding the right phenomenon to couple with.

When our group began its first serious venture into biology (*1*), it was realized that the issue of chemical oscillators was a question more fundamental than the way it first may appear to chemical engineers in the process industries. The chemical process industry issue is used as an analogue because both the practitioner of that field and the biochemist are dealing with a complex autonomous chemical plant (and they may both view oscillations, at first, as simply being a parasitic nuisance).

The issue of the chemical oscillator was clarified to us when a chemical engineering colleague called out attention to a chemothermal oscillator (*2*). The problem, we realized, was the broad common problem of nonlinear stability that we had been pursuing in other fields (*3*, *4*, or *23* to *26*).

At that point in our education, we finally realized that a chemical oscillator did not have to be a pure sequence of chemical steps (for example, a group of chemicals oscillating in concentration in a beaker) but could arise by coupling of other than chemical steps to chemical steps. As we will discuss, there was still a missing step in our understanding of what might be required for a biochemical oscillator.

Regardless of what the system is coupled to, the problem remained one of finding a coupling with a chemical process step that would make the overall process linearly unstable, but nonlinearly stable as a limit cycle oscillator (according to nonlinear mechanical concepts) or a thermodynamic engine cycle. (In thermodynamic concepts, a system that could enter into a cycle of performance by transforming from some constant potential source of energy into energy in transit is an engine.)

With regard to the biochemical oscillator, one major line that has stimulated the question of the biochemical oscillator has been the nature and origin of life. For example, using him as a protagonist, Pattee (*4*) has suggested that the central question requiring explanation for the nature of life is its hereditary property, "the potential for hereditary evolution is the primary characteristic of life...." He asks what this means in the language of physics. He rejects the view that life "is just a certain collection of DNA, RNA, enzymes, and other molecules in the proper spatial configuration." The organization of molecules by physics is known to require only a few forces. As yet no combinations of such forces are known which can be uniquely associated with living organizations. Thus he points out that "molecular biologists tend to... underestimate the exceptional physical requirements for persistent hereditary processes...."

We submit that Pattee's hereditary processes ("Hereditary processes require the existence of a set of relatively fixed objects or traits any one of which can be transferred in a recognizable form from parent to offspring in the course of time") represent periodic processes; that is, there is essential need for biochemical oscillators. Detailed reading of his material suggests that Pattee expects that problem to be solved at the molecular level (for example, considering a simple hereditary tactic copolymerization "...in such a copolymer, hereditary propagation must depend on specific catalytic control of the rates of monomer addition...." Then, later, in discussing whether classical nonholonomic machinery can exist reliable enough to assure persistent hereditary evolution in a noisy environment, his basic criterion for life, he concludes that they can't because "The elementary rate-controlling or logical machinery of living systems are not macroscopic organs but individual molecules—the enzymes." Classical machines would have high error rate. On the other hand, living cells execute their hereditary rules with reliability by using single molecules. He concludes, thus, that the dynamic behavior of enzymes, as hereditary elements, cannot be described by classical models).

However, not all biophysical investigators have been willing to wait for the development of biochemical or at least chemical oscillators at a purely chemical-molecular level (that is, what might be referred to, even if catalytic molecules are used, as *chemo-chemo coupling*).

The reader may note the logical picture that faced us after our first biological review paper (*1*). It was clear that self-maintained oscillatory processes were intrinsic to biological systems. Actually, a precursor to that review was work we had done on the human body as a thermal source in evaluating the effectiveness of clothing in providing insulation. The issue was that in order to relate the thermal fluxes, temperature potentials, and impedances by an ohmic relation, we had to recognize that the source is an active inconstant source; namely, the human is a thermodynamic engine, but its internal combustion processes had not been dynamically evaluated. Experimentally we found a spectrum of large power oscillations within the body system, with periods of 2, 7, and 30 min. and 3½ hr. Thus, in addition to the well-known heart beat (which had been analyzed as a nonlinear relaxation oscillator by van der Pol), the breathing oscillator, and unit electrical processes such as brain waves, we now added basic metabolic oscillators.

When we began our 1962 review of control in the biosystem, we quickly found the central principle in biology enunciated as homeostasis, representing a regulation of the internal variables in the system (its fluxes and potentials) independent of conditions external to the complex organism. It seemed clear to us that such regulated states require mechanisms involved in dynamic regulation or control. It was such description that we found lacking in the biological literature, except for a few isolated instances. (To cite two: the modeling of

Danziger and Elmergreen of thyroid function, and of Yates and Urquhart of adrenal function.)

Having our own observations on the oscillating nature of metabolic processes to add to known periodic processes (heart beat, breathing, EEG, alternation of rest and wake) we began to trace out a broader spectrum of autonomous oscillators in the complex biological spectrum. For example, we have found oscillations in other metabolic constituents in blood: blood sugar, blood gases (oxygen and carbon dioxide), lactate, free fatty acids, even in the file of red cells in capillaries.

Seeking function and structure beyond these oscillatory processes, we then expected to be confronted with the identification of the regulators and controllers. However, it finally dawned on us, as we uncovered the ubiquity of large amplitude oscillations, that in toto the network chains from which the oscillations emerged likely made up the biological system. Coupled with mechanisms embodying their control algorithms, functionally they represented a dynamic scheme of regulation within the body for which we have proposed the name *homeokinesis*. Homeokinesis denotes the scheme of mediation of the operating conditions of a large but compact collection of coupled autonomous oscillators, mainly by inhibition or release from inhibition, so that their mean state provides near constancy of internal variables.

Thus, our biological theme came to rest within the identification of those dynamic causal chains that make up the many spectral lines to be found in the biological system. We view the approach as biospectroscopy, or dynamic systems analysis. We have discussed a number of these chains in various references (*4*, 7 to 9).

At the same time, many molecular biologists and biophysicists became increasingly interested in conditions for the operation of a chemical oscillator (*5*). Much of the impetus was directed toward foundations for the theory of life, the living process, and the origins of life.

When we enunciated the oscillatory nature of macroscopic processes in the biological organism, we viewed these as being one parallel track of dynamic systems analysis in a hierarchical ordering. As physical scientists we, of course, had grown up with the spectroscopy of atoms. There was a missing link at the molecular level of chemical oscillators. We were pleased when we discovered the work of Goodwin (6), who clearly enunciated the character of the cell as an oscillator system. We, of course, were content with our complementary contribution to the macrodynamics of the entire organism and then in extension to the macrodynamics of behavior (*7*, *8*, *4*).

There remained the problem associated with the chemical oscillator. There were no theoretical grounds to exclude the possibility; only the question of under what conditions could one be formed. It was clear that it could be done on a macroscopic scale by coupling with other phenomena.

It finally occurred to us from the work of Britton Chance on metabolic oscillators in cells and ours on total body metabolism, that much of the problem was a matter of scale. Very much as in the fractionating column, it is a matter of field size of competing phenomena to get a particular dynamic reaction to come off and provide substantial yield, that is, to entrain a process into sustained operation. We were pleased to find such views suggested by Scriven (*4*). We stressed it as cooperative phenomena (*10*).

It remained for Katchalsky, at the 1969 International Biophysics Congress, to point out that the chemical engineers already had arrived at some of the theoretical pieces for simple catalysis. They are contained in two parameters associated with catalysis, the reaction length and the coefficient of anisotropy.

Many of the issues came into focus at that Congress in a session on the origins of life, notably in Katchalsky's reports of his and Zhabotinsky's work toward a chemical oscillator. The work of Zhabotinsky is finally becoming available. The first easily accessible report is in Nature (*11*), the catalytic oxidation of malonic acid by potassium bromate with cerium trisulphate used as catalyst. In discussing the problem of achieving a chemical oscillator, in work that he had done in achieving high polymeric peptides, Katchalsky referenced the prophetic words of Bernal for the possible significance of clay as a primeval stratum for the origin of life. More important, he demonstrated a scale of about 1,000 Å (using a swelling clay, montmorillonite, as a *p*H sensitive stratum for the polycondensation process).

At the second International Conference on Theoretical Physics and Biology (*12*, *13*), both Katchalsky and Prigogine start their discussion of the chemical oscillator (as a lead in to the biochemical oscillator) from the hydrodynamic modeling of rapid flow, inhomogeneous, dissipative processes. They regard the Bénard cells of Scriven (*4*) as a prime example of such hydrodynamic instability producing dynamic form.

Katchalsky: As "... the 'central dogma' of molecular biophysics all information about... structure and function is coded in DNA and the phenomena of life is only the unfolding of the genetic script. Granting that the dogma may be accepted literally, the dynamics of biological structures still remain an open problem... Structuring and maintenance of flow patterns through the coupling of macroscopic flows is well known in classical hydrodynamics....

"The recognition that the coupling between chemical reaction and diffusional flow may also lead to instabilities and the formation of dynamic patterns is due to A. M. Turing...."

"The classical hydrodynamic example of the maintenance of dynamic structures is the phenomena of Benard discovered in 1900...."

Here an argument begins. At this moment, the only sustained oscillator we know of is the Bush example. It is not clear yet whether oscillations will continue indefinitely in the Zhabotinsky examples. (Many people are repeating and elaborating the work; our intent is not to challenge the possibility but rather the scope of the interpretations.) We are not aware whether Chance has yet shown oscillations that will persist indefinitely.

In our opinion it is invalid to expect chemical oscillations out of simple rate kinetics and diffusion in chemical reactions. This was precisely the problem we tackled 20 yr. ago for C. E. Mason and described most generally as equivalent to propagation in an inhomogeneous R-C line.

The question of whether a molecular catalyst can locally produce an inhomogeneity capable of producing a local oscillator (for example, a local biochemical oscillator) brings us up to Pattee's question. We (and we surmise that Pattee would agree) don't know the answer. The requirement for a high hereditary determinacy is very difficult.

Now with regard to adding rapid flow processes to the prescription, as Katchalsky and Prigogine and Scriven (and we believe Morowitz) have done, we have some added comments. Here the issue precedes Benard, going back to Reynolds, and the maintenance of a turbulent field. A selected list of classical references of literature on hydrodynamic stability (some of the early sources, and more recent) are offered (*14* to *22*). Some of the contributions of the author to the quantization of the hydrodynamic field are also listed (*23* to *26*).

We offer a different but very parallel criticism to Pattee's. Our experience with the hydrodynamic field suggests that wave propagation is often a necessary ingredient to bring a hydrodynamic oscillator into being. We remind the reader that the Reynolds number is the ratio of inertial to viscous forces, and it takes a critical ratio to bring turbulence or any other flow structure (G. I. Taylor cells between rotating cylinders, Bénard cells, the Richardson instability) into existence.

It appears to us that the combination of a degradative process of viscosity, the inertial forces (for example, L-C, mass-spring, rotational inertia, buoyant density, density gradients—see the classic argument conducted by Rayleigh, seeking instability via inflection points in the mean flow profile as compared with Reynolds' search via a viscous mechanism, and Lin's subsequent discussions), inhomogeneity in the field, and the nonlinearity (generally introduced by convection) can lead to hydrodynamic oscillators.

An alternate ingredient for instability that may lead to an oscillator is a mechanism selected from another hierarchical level. The names of some typical devices that have been used are negative resistance characteristics, hysteresis characteristics, Monod-Changeux conformation characteristics, snap-diaphragm action, tunnel diodes, clock escapements, or (as hoped by Pattee) suitable quantum mechanical nonholonomic constraints.

The idea, generally, is to work out a nonlinear chain which is clearly linearly unstable and which can feed from a potential energy source. Poincare used the snap-diaphragm as a static illustration of instability. It is analogous in concept to the Monod-Changeux mechanism. However, a snap-diaphragm will not create an oscillation by itself. As with all negative resistance devices, they are commonly yoked with an inertial system, so that the overall nonlinear system will continue to oscillate. Whether we have simply deferred the question of a need for inertial forces as well as nonlinearity to another level is not clear.

We identify this as reference to another hierarchical level because (illustratively) a negative resistance cannot be constructed at the same hierarchical level as simple passive positive resistances. There it violates the laws of thermodynamics. But by constructing ingredients for a thermodynamic engine from another level, they can be brought in without any overall contradiction. Loosely put, it is function at one level that can provide form or function at another level. If there is one level at which periodic function can be achieved, then it is possible for it to be achieved at all levels. In our cosmology we have the interconversion of mass and energy in the universe as a primary oscillator source (*3*).

Thus, Pattee's uneasiness about biochemical oscillators is buried at the level of finding a suitable nonholonomic constraint at the molecular level, ours of finding one at another hierarchical level which can be coupled to the basic level. We both are in favor of suitable substrates for sustaining the reactions.

In our opinion, Bush has found a suitable substrate, the coupling to a thermal boundary layer that provides the escapement. We are intrigued by Katchalsky's use of clay substrate which by periodic swelling and relaxation can act as an escapement. Such or similar substrate paths ought to be able to lead finally to biochemical oscillators. But they must be found as specific dynamic escapements. The static conditions, the double helix and other details of molecular arrangements, may be necessary conditions, but they do not, of themselves, create the dynamic conditions for sustained oscillation.

The important contribution of Katchalsky, we again note, is that he demonstrated a scale, at near solid state domain size (1,000 Å) rather than molecular or macroscopic size, which may be conducive to producing an oscillator. A concluding thought for chemical engineers interested in biological control might be that as the past 25 yr. have demonstrated in many ways, one may not be able to estimate in advance the size of the volume or beaker that one can use as a unit cell in some continu-

ous flow relaxation process, in this case the crucible for life processes themselves. He must guide himself accordingly as he seeks the unit processes in the biological system.

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