Biology and mathematics. Recent developments in the areas of biological research stimulate increased interest to oscillatory chemical processes. And increasing number of researchers seem to believe that the basis for the complex organizational structure of the processes that take place inside living organisms lie in oscillatory chemical reactions. As it is usually the case in growing areas of science, there are as many supporters as there are opponents of this point of view. Mathematicians’ persistent attempts to analyze this phenomenon from their point of view is very characteristic of the general state of active analysis of this rich biological material.

Let’s try to understand what it is that mathematicians are trying to do. It makes sense to expand the question and to talk about what the place of mathematical methods in biology is in general. The crucial role of mathematics in physics, for example, is very well known. Theoretical physics is largely a mathematical science. However, in chemistry the role of mathematics is not nearly as great and it decreases progressively as one “approaches” biology. Until very recently statistical analysis of data was the only instance of “mathematical presence” in biology. A biologist used mathematics to “polish the surface” of a biological fact and then “disposed” of it along with experimental “leftovers”. A thought that mathematics could also be of use on the “purified” stage of his work would not even cross his mind. Pure mathematics, that is.

A little bit about cybernetics. New light is shed on the whole situation now that it has stabilized a little, making one capable of making some preliminary conclusions. It seems that it is biology that has penetrated technology, and not vice versa. Technology got enriched with many ideas, and cybernetics had a lot to do with that. However, reverse process also took place, although to a much lesser extent - unfortunately, action is not always equal to its counter-action. Noticeably, we are now talking about the ideological effect, about the influence on the perception of theory and not about the creation of new technological research methods.

Darwin and Clausius. To understand what has happened one first needs to review some history. It is at the end of the last century that the main ideas of classical physics and biology were formulated. In physics it was the triumph of the atomic theory and a closely related reevaluation of understanding of the world structure from a statistical point of view. Darwin’s theory of evolution established its place in biology. Thermal death of the Universe on one flag and the process of endless perfection in the other. There was plenty of room for appearance of mutual misunderstanding that would last for many years. Sooner or later these two points of view had to collide. In reality, they had long started colliding in the minds of some of the most prominent physicists of the time. Boltzmann
himself introduced the idea of enormous fluctuation. He was quickly “denounced” - a much smaller fluctuation would be much more “probable”. Back then there was nothing one could say to argue with that. It is much more surprising that Boltzmann’s hypothesis is still considered unsound. After all, since then we have found out that space-time (quantum physics vacuum) is a balanced form of the existence of matter; that substance (including radiation) is a nonequilibrium form of matter and that the phrase “enormous fluctuation” simply means that the Universe is rich enough with matter to be able to have fluctuations of this size. There simply could not be smaller fluctuations since very small deviations from equilibrium are as “unlikely” as very large ones.

One should not think that it was only the ideological differences that stood in the way of mutual enrichment between biology and physics. After all, the physicists of today seem perfectly fine with inner controversies in their theories, and numerous absurdities that came from blind faith in the power of the new methods did not stand in the way of development of mathematical analysis. “Go forth, confidence will catch up with you” is the typical motto of Romantic periods of the development of science.

Nonlinearities in biology. Ideological differences were a more obvious form of the deep methodological contradiction between biology and physics, a contradiction that came from the core of the problems that these sciences were trying to address. The gap between them is far from being closed even now, but at least now it is possible to appreciate its magnitude.

One of the most characteristic properties of biological objects is the enormous range of external forces, despite which the system remains functional. Normally biological systems are not just nonlinear but, if one can say so, exponentially nonlinear, a phenomenon that is most probably caused by cruel necessity. Logarithmic scale of answers is the only way to capture all informative and significant forces, while maintaining a reasonable organ size. Systems that are incapable of this have failed in the competition for survival.

This is the case in biology, and in physics this was not the case until just very recently - at least in terms of the mathematical apparatus used in physics. Principle of superposition, independent fluctuations, eigenfunction expansion, perturbation theory are all just different expressions of one main conditions. In physics it is mostly the small perturbations from equilibrium that are studied, and so the theory is mostly linear. Importantly, even “the” principle of the increase of entropy is tightly connected to the idea of additivity of energy. Additivity is a much more profound concept than that of linearity, although they are related. Notably, it is the study of very simple systems, whose organization could for the most part be neglected, that gave rise to both of these concepts.

Substantial insufficiency of the linear approach in physics became evident, as usual, when it came to practical matters, radio engineering in particular. That is not surprising - nonlinearity will always appear in most mechanisms that “conjugate” technical systems with biology. It is through radio engineering that the nonlinear methods of mathematical applications really started developing (suffice to recall the names of such people as Mandelshtam or Andronov).
For a relatively long time the forced rejection of the linear “way of thinking” in any practical matters peacefully coexisted with the most absurd theoretical notions (such as “inevitability of the destruction of the Universe due to overheating”).

Entropy increases. What does it mean? An important step to understanding the notion of entropy was taken in the works by A.Y.Khinchin, especially in his book “Mathematical bases of statistical mechanics”, which was published in 1943.

In this book it is shown that the basic notions of thermodynamics, such as temperature and entropy, become scientifically accurate only for extreme, idealized systems, which have the following properties: 1. The system consists of a large number of separate subsystems (particles). 2. The system is closed, i.e. there is no energy exchange with the outside. 3. The total energy of the system is equal to the sum of energies of separate subsystems. 4. The system exists in the state of statistical equilibrium.

A propos, from this one can actually see that the title “thermodynamics” is in itself disorienting. One should actually talk about “thermostatics” since all the conclusions pertain to the system’s equilibrium states. Khinchin shows how to define the notions of temperature and entropy from a statistical point of view and proves the following theorem:

Temperature $T$ of a two-component system in equilibrium lies between the temperatures of the components $T_1 \leq T \leq T_2$. Entropy $S$ is greater or equal to the sum of entropies $S \geq S_1 + S_2$, and the equality is achieved only if $T_1 = T_2$.

This is the theorem that has often fallen subject to the following type of interpretation: at first the entropy was $S_1 + S_2$, and after the system has reached equilibrium it became $S$. Since $S \geq S_1 + S_2$, “fatal degradation” of energy is evident. However, in this argument it is still assumed that 1) the notion of entropy makes sense when the system is out of equilibrium and 2) even in this case the total entropy of the system equals the sum of entropies of the subsystems.

Critical analysis of such “enhancements” of the formulated theorem lead Khinchin to believe that all of them make indirect use of statements that are in fact equivalent to what is being proven (something along the same lines as the numerous “proofs” of Euclid’s fifth postulate). Notably, nothing in the theorem says how soon equilibrium is achieved and whether it is achieved at all. Rather, the theorem states that “should the system reach equilibrium, then these would be the correlations that would follow”.

Statistical equilibrium and ergodicity. Much of Khinchin’s contribution lies in the fact that he has drawn a clear line between two completely different notions: achievement of equilibrium and calculation of the characteristics of a system that is already in equilibrium.

The second problem is much simpler and can have a full solution, achieved through a number of methods. In particular, Khinchin himself suggested a rather elegant approach - the theory of summatory functions - that is analogous to the mathematical apparatus of the theory of probability. It is plausible that minor improvements to this method would allow to give an account of both the special cases of one theory and of such diverse questions as information theory, classical and quantum mechanics, talandric thermodynamics, thermodynamics of small systems and nonequilibrium processes, from one point of view. Despite the heterogeneity of these problems they all share the same patterns of mass phenomena
that are largely determined but the sheer fact of the “mass character” and depend much less on the specific properties of each particle.

However, let’s get back to discussing the main question of achieving equilibrium. The state of statistical equilibrium that everyone talks about is qualitatively different from the “habitual” equilibrium states of the simple mechanical processes and physical systems. It does not imply lack of movement or lack of desire to reach some kind of an asymptotic state. That is the state of the dynamic “mobile” equilibrium of the system as a whole. Persistent efforts to understand this difficult question have a long history and gave rise to a large and rich body of literature. The first step was taken by Boltzman, who suggested (ergodic hypothesis) that a point in the multi-dimensional space (phase space) that depicts the momentary state of the system goes though all points of the phase volume that is compatible with the given values of the external parameters and energy. It soon became clear that it is mathematically impossible, and so the ergodic hypothesis was modified, stating that the trajectory could come arbitrarily close to any point - the trajectory is dense everywhere.

If this statement were proven, then the main property of the states of statistic equilibrium - the fact that thermodynamic quantities remain constant - would become clear. Mathematically, a thermodynamic quantity is the average in time along the system trajectory of a corresponding phase function. For instance, pressure is the average of the sum of impulses. So, if the trajectory is uniformly dense, then one can say that the average over time of every phase function is equal to the average over space. Thermodynamic functions then become the average over space, and so it becomes clear that they do not depend on the trajectory. It is a beautiful and well-known statement. The problem is, someone has yet to prove the ergodic hypothesis in any sort of a general case.

The role of atomisticity. The progress in this issue was actually made in the works of Khinchin himself, and it is the formulation of the question itself that has undergone the most substantial changes. Followers of the ergodic theory are mostly concerned with the very tricky behavior of the phase trajectory. Khinchin sees the major problem to be in the properties of thermodynamic quantities, particularly in the fact that the functions that give rise to them are actually nearly constant themselves. This is a beautiful way to look at this problem, since looking at a problem in an unconventional way is often the most difficult thing in science. One should have a lot of courage to dare and infringe on the traditions. It’s not surprising that Khinchin’s ideas are still relatively unknown, and that is not due to the limited edition of his book.

So which properties of thermodynamic quantities allow such radical simplification of the question? There are two such properties. One deals with the fact that the corresponding phase functions have a very particular algebraic structure. Their dependence on the coordinates of each individual particle may be as complicated as it likes but their dependence on different particles is very simple - it’s the sum over all the particles. The second important property of thermodynamic quantities is that they are sums of an enormous number of components, since the nature of the problem lies in the study of asymptotic properties of the systems, which consist of a large number of identical objects.
Then, the center of gravity of the problem shifts to the study of the properties of the functions, and Khinchin proves that summatory functions have the following beautiful property:

Consider one arbitrary summatory function (for instance, energy). Assume that its level curves bound the regions that have finite phase volume. Now also consider any other summatory function. It turns out that the second function is also nearly constant on each level curve of the first function. To be more precise, it can, and it will, be significantly different from a constant on the manifold of the set of measure of the order $1/\sqrt{n}$; however, on the rest of the manifold this difference will be very small.

There’s more than one temperature. One should not think, of course, that the “ergodic” way of thinking is completely irrelevant. It is in fact very much relevant since it can happen that the trajectory actually does lie on a very particular manifold. It is likely to happen, for instance, when the system of equations has some other integral of motion in addition to energy. Then the entire trajectory lies on the intersection of this new energy and on the level curve of this new integral. The intersection forms a dimensionally smaller manifold and consequently is a set has measure zero.

The calculations in this case are still based on the notions of the theory of summatory functions, except in this case one needs to take not one but two summatory functions. As a result, all the other summatory functions become functions of not one but two variables (e.g. not just temperature like in classical thermodynamics but temperature and, for example, chemical potential).

It may seem that we just got back to where we started: we need to find and average over a manifold, where the trajectory is uniformly dense. This is not exactly the case. Theory of summatory functions actually shows that, firstly, the functions are nearly constant even before averaging and secondly, loosens the necessary conditions for the trajectory. It is no longer essential that the trajectory be dense; what is important is for it not to be “stuck” in any particular set. Previously one had to prove that the trajectory passes through every region and stays there for a period of time that is proportional to the volume of the region; now, it suffices to show that closure of the trajectory is not a set of measure zero. But this extremely relaxed condition one does need to prove. And we are talking not about a rigorous proof (which in any case would be nice) but about making sure that there exist no additional integrals that could significantly change the result. After all, don’t forget the edifying story of the theory of heat capacity, which has cost physicists much grief and confusion. The situation got resolved only after the creation of quantum statistics (symmetric and asymmetric); on top of everything it turned out that classical statistics corresponds to the averaging over the entire phase space (which is infinitely dimensional!), and new statistics come up in averaging over manifolds of measure zero (manifolds of symmetric and asymmetric functions).

“Vast” majority and “insignificant” minority. Before we conclude this protracted digression into statistical problems in physics, we need to discuss one more question that is directly related to the main topic.
Until now we have talked about the properties and behavior of the system as a whole. The same mathematical results, however, allow for certain ambiguities in interpretation if we consider the behavior of individual particles.

Maxwell’s distribution for speed of the molecules is an example of such interpretation. From a purely descriptive point of view, the statistics shows that the characteristics of a vast majority of the particles lie within a particular interval around the average values, and an “insignificant minority” of particles (of the order about \( \sqrt{n} \) out of \( n \) total particles) can and will deviate from the norm. It is very important to note that even though interactions between particles are not formally considered in the simplest statistical scheme, it is in fact the sole factor that can provide the necessary particle mixing. Moreover, these interactions must be “resilient” in character, is an exchange of mechanical energy. This last requirement, which is very difficult to formulate exactly for general (non-mechanical) systems is in fact extremely important. It shows immediately that thermodynamic notions make sense only when time is “small” relative to the time that is necessary for non-resilient interactions.

One should never forget about this little detail, or our ears will be unpleasantly surprised by the cracking of bones of the “vast majority”, voraciously engulfed by the “insignificant minority”. It is possible that something very similar happened during the evolution of the “could of dust”, which some believe to have been the precursor of our solar system. Thermodynamics “goes extinct”. Let’s move on to some important conclusions about the place and the relations of entropic and evolutionary perspectives. Before we move on it’s important to note that while until now we were mostly talking about results, now we unfortunately will have to deal much more with speculations and suppositions. However, that’s the state of affairs in theory, and a general methodological analysis is necessary to evaluate what has already been done and formulate reasonable questions for future work.

It was not uncommon in the history of science that two seemingly opposite and even mutually excluding points of view have later turned out to be just extreme, polar cases of the big picture. Niels Bohr has even promoted the principle of complementarity if not to the rank of the law of nature then at least to the law of knowledge. One can spend a lot of time arguing about the meaning of this principle but the sheer fact of its existence is quite symptomatic. It shows the importance of pairs of polar concepts in science, such as wave-particle, or deterministic-stochastic.

Let’s try to argue that entropic and evolutionary concepts are also an example of such a polar pair. As of now we cannot yet formulate this statement in any rigorous way but that just means that it will be one of the theoretical problems to be addressed in the nearest future. However, looking at a number of diverse enough examples does simplify correct formulation of the question quite a bit.

Let’s look at the evolution of “the dust cloud” as one such example. At first it consists of a large number of separate particles, and so statistical and thermodynamic concepts are very much applicable to it. It is important that the volumes considered be large enough to contain large numbers of particles (let’s not forget that \( \frac{1}{\sqrt{n}} \) if the measure of applicability of thermodynamic theory) but small enough for all the particles to be in a homogeneous
environment. Since the particles interact often and rarely clump, all facts speak for ergodicity. Particle clumping may happen slowly and infrequently but it happens nonetheless. The system goes through a number of states, and each state is statistically at equilibrium; the number of particles decreases, heterogeneities increase, and the organization gets more and more complicated. Notably, for our purposes it is not important whether this is really the way that our planetary system came about. We are talking about a “mental experiment”. Let’s look at the final stages of evolution. Big planets have been formed and are now moving like clockwork (they are actually the prototype of how a clock will later be built). But what happened are statistics and thermodynamics? Despite all the naiveté of this example, it does show the main point: applicability of statistical notions decreases with evolution, since the number of particles decreases. Thus, we arrive at a paradoxical conclusion - in this case thermodynamics is applicable at early stages of evolution, while it is mechanics that comes into play when we need to describe the state of evolutionary maturity.

Areas of applicability of thermodynamics. However, taking a moment to think about this in more depth can show that the last statement is not so much of a paradox after all. One just needs to remember that the question of interactions lies outside the scope of thermodynamics. Let’s formulate the question in the following way. Assume that equations that describe exactly the behavior of some system are known. Then the main terms in these equations will be the ones that determine the behavior of each particle in their environment. The interactions are going to be insignificant compared to the main terms, out of which the terms that describe resilient coupled interactions. Moreover, there exist also extremely small terms that account for the process of dissipation and even more complicated processes of non-resilient interactions, such as chemical interactions that can lead to the disappearance of old particles and appearance of new ones. In correspondence to the three types of terms there are now three time scales: small time scale, at which separate particles behave like free particles; large time scale, at which several jolts happen, and extremely large time scales, of evolutionary magnitude, where extremely small, non-resilient terms start to play a role. It is worth noting (for comparison purposes) that during typical chemical reactions in the gas phase there occur from $10^{10}$ to $10^{11}$ resilient collisions per one effective “chemical” collision. How will such a system behave? Let’s skip the not so interesting stage of small time scales, where nothing really happens. At the next time scale one can still neglect non-resilient terms but it is the resilient terms that play a major role here. This is the time scale, where true static equilibrium is achieved and where statistics reigns, stemming on a conceptual level from the fact that the particles at all time preserve the “individuality”. It is important to note that all “entropic” discussions implicitly make use of actually inappropriate in this case extrapolation to the evolutionary times of patterns that are undoubtedly valid but on different, much smaller, time scales of thermodynamic relaxation. The correct conclusion would be the following: usually evolution is a much slower process, which happens on the backdrop of stable and slowly shifting thermodynamic equilibrium.
On mathematical models. The methodological analysis given above seems to justify the necessity for formulation of more general theory that would both the principles of entropy and evolution as critical, or “limiting” situations that an evolving system can be in.

Let’s try to outline the main traits of the processes that are characteristic for any evolving system, whether biological, chemical or physical, and which due to their generality could make a good basis for building of a mathematical model.

Since it should be evolutionary theory, i.e. theory of changes that happen over time, theory of differential equations seems like the most applicable mathematical apparatus. For the time being we can even narrow it down to ordinary differential equations $\frac{dx}{dt} = A(x)$ that already provide quite a wealth of possibilities.

One can also look at discrete and partial differential equations as critical cases of ordinary differential equations. They can undoubtedly be more appropriate in particular problems but algorithmically much more developed ODE theory will suffice for general conclusions (provided also that mathematicians are quite skilled in “generalization industry”, finding ways to apply results from ODEs to PDEs and difference equations). The equations should be autonomous, i.e. the right hand side must not explicitly depend on time $t$. This means that the state of the system at time $[x(t + \delta t)]$ is defined solely by its state $[x(t)]$ at time $t$, independently of the state of the outside world.

The system is thus “informationally” closed. In all other aspects (for instance, from the point of view of energy, it can very well remain open but it is the system that decides what and when it will take from the outside world or give to it.

Next important property is atomisticity of the construction. There are two aspects that are important for it. One is that the number of particles (individuals) is very large. The other is that particles are largely independent of each other. In the context of a mathematical model, the first aspect implies that vector $x$ has enormous dimensionality (for instance, it is $6n$ for a case, where $n \approx 10^{19}$ if we are talking about one cubic centimeter).

Particle independence in a mathematical model is accounted for by a special form of the equation’s right hand side. The equations contain the small parameter $\epsilon$ in such a way that at $\epsilon = 0$ the system splits up into independent equations, each of which describes the behavior of each separate particle. The system of equations then takes the following form:

$$\frac{dx_i}{dt} = f_i(x_i) + \epsilon F_i(x_1, x_n).$$

Each variable $x_i$ that describes the state of $i^{th}$ particle is of course a vector, perhaps even one with a large number of components. It is reasonable to assume that the system is composed of particles of two or three types. In particular, it is reasonable to assume that among the functions $f$ there exist two or three qualitatively different functions (they might even depend on a different number of variables) but within each type these functions differ only by the index $i$. 
Further specification deals with the nature of interactions, i.e. with the properties of functions $F_i$. In any case one should start with looking at just the coupled interaction

$$F_i(x_1, x_n) = \sum_{k=1}^{n} F(x_i, x_k).$$

It is reasonable to believe that all possible phenomena are already contained in the model of coupled interactions, at least qualitatively. As a result, the system becomes:

$$\frac{dx_i}{dt} = f(x_i) + \epsilon \sum_{k=1}^{n} F(x_i, x_k).$$

One could also make an argument for further model simplification but now is not the place for going into this much detail.

Evolution takes a step. What would the theory of such a model look like? (We hope our mathematically oriented readers will forgive us for the giddy leaps of logic, and our biologically oriented readers - for unusual poverty of the resulting scheme, but we will still try to present a number of statements that outline the possible theory).

Generally speaking, evolution of such a system consists of three qualitatively different stages.

The first stage is establishment of statistic equilibrium - broadly speaking, it is a thermodynamic stage.

The second stage is the slow evolution that goes through a series of thermodynamically quasi-steady states. The evolution ends with creation of conditions for the new type of individual particles that are qualitatively different from the original ones, which leads to the third stage. At the third stage happens the so-called “explosive proliferation” of the new particles, when the number of particles grows exponentially quickly (on an evolutionary time scale, of course). An alternative possibility would be loss of stability by one of the “types” and its subsequent disappearance. This stage ends with exhaustion of resources for the creation of new particles. “Type disappearance” does not necessarily imply its extinction. It very well could be a transition to a new level that would correspond to the new outside conditions.

As a result we end up with a scheme that is analogous to the one that we started with, except some of the old types have disappeared or gone extinct, and new types were created, often with a new time scale (time of “life” span of one individual or particle). Noticeably, the new system is thermodynamically out of equilibrium, since the particles in it are now different, and in a way, the thermodynamics is now different (recall the law of partial pressures in regular thermodynamics that states that each gas occupies the space that is filled with other gases as if it were empty; the new “type” can very well behave in a similar fashion). Clearly, if the suggested system does correspond to what actually happens, then purely evolutionarily or purely thermodynamically driven scenarios are idealized limiting cases of a more general layout of an evolutionary cycle. It is probably better to speak of “evolutionary step”, since the system has undergone serious changes, and the word “step”
is semantically flexible enough to be able to mean not only staying in one place but also moving forward. And backwards.

Dispersion, evolution, explosion. Let’s look at all the different stages in more detail. All three stages are equally important, and each could be seen as the beginning of the cycle. Let’s start with the first stage, which has been called first solely out of respect to the history of science.

For the considered systems it is possible to build a theory of statistical equilibrium that is analogous to “regular” thermodynamics. However, the main difference will lie in the most important idea. The state of equilibrium is characterized not by one “inner” parameter, as it would be in case of only one energy force, but by several numbers. Temperature starts to resemble a vector. Of course, there is nothing extraordinary about that. In chemical systems, for example, it is necessary to know chemical potential in addition to the temperature, and its role is as important as that of temperature.

A general outline for the development of this theory for “two-dimensional temperature” was given above.

The next point is the most difficult in the entire program - it is finding the conditions, under which the interactions can lead to statistical equilibrium. The fact that the matters are in about as bad a shape in statistical mechanics despite one hundred years of its existence does not provide much comfort. But one thing is clear - not every type of interaction leads to statistical equilibrium. One should not think this fact to be purely negative. On the contrary, it is possible that it is in fact one of the mechanisms of “cutting off“ the side branches of the tree of evolution.

Next comes the stage of slow evolution of the state statistical equilibrium. Here one could give a truly enormous number of very diverse examples (Outer layers of a star are in a state of rather complicated thermodynamic equilibrium. As the layer of hydrogen combusting to helium (for hydrogen-based stars) approaches the surface, the outer layer of the star seems to become very unstable. This can lead to an explosion that leads to oscillations, or to oscillations that lead to an explosion - both points of view are out there). One should note that the well-known theory of irreversible processes deals with a very simple idealized example of the theory of evolution of the equilibrium state, the case when linear approximation to the problem will suffice.

It seems like the appearance of conditions that can lead to the formation of new species is the question that is of utmost interest for biological applications. Clearly, there could be a number of different cases. When conditions necessary for exponential growth appear, going through a critical point is what happens most often (very typical examples are chain reactions, as well as many infectious diseases). The new particles could have been appearing throughout all the previous stages of evolution but if before they would disintegrate before having a chance to multiply, now the new “species” manage to stick around.

On the subject of resonance. The most interesting question is - how can we mathematically model appearance of a new particle? Let’s look at one possible way. Let’s consider the new particle to be two (or more) old particles that have formed a coalition. It could be adhesion of these particles, which would cause them to have very close spatial coordinates at all times, but this case is not too interesting.
A much more interesting possibility for the formation of particle coalition is the resonance of oscillating systems. Modern physics considers this way to be so important that a new term (not a very good one, though), has been coined for this process - “resonon”. ** One could give many more reasons for why resonance-induced formation of new particles makes such good sense but “he who proves too much, proves nothing”. Let’s therefore look just at an encouraging example of linear theories. If even such simple assumptions allowed systematization of so much material, one could expect nothing less from the theory that takes non-linearity into account.

*Darwinism and exact sciences.* Let’s summarize the main ideas. First consideration. Modern mathematical apparatus, which was created in close contact with and under direct influence of classic physics, needs to be seriously upgraded even when dealing with modern physics, is very poorly suited for dealing with biological problems. That’s why interactions with biology, which are inevitable if one is to try to “apply” mathematics to biology, should enrich mathematics above all. And it is mathematics that should learn its lessons from inevitable failures and semi-successes. “First the hands teach the head, and then the head starts teaching the hands”.

Second consideration is basically just a concretization of the first consideration. Darwin’s theory of evolution should take an appropriate place in exact natural sciences. By now enough facts have been gathered to show that main principles of Darwinism are applicable to all evolving systems, from elementary particles to galaxies. Unfortunately, “applications” are usually mostly illustrative in nature: once a new theory has been created with specific methods, one can observe, with satisfaction, that everything resembles biological evolution quite a bit. Meanwhile an enormous creative force is rooted in Darwinism - the idea of the organizing potential of the large periods of time. And it is the mathematical formalization of theory and the liberation of ideas from their narrow, overly specialized expression that can uncover its universal importance.

The program that was formulated above is one of numerous attempts of such generalization. What allows us to hope for some progress (which, of course, can only be evaluated after the realization of the program) is the simplification of the problem, with a focus shifted towards “extracting” the evolutionary cycle. The resulting problem could then be formalized, while still hopefully preserving the most important properties of the evolutionary process.

The notion of an evolutionary cycle gives clear formulation of the idea that every evolutionary process, regardless of its complexity, can be subdivided into much more simple cycles that supersede each other. In a way, it is the idea of discreteness, of atomisticity of evolution that is of most importance here, putting particular emphasis on the notion of “species”. The cycle begins with the “dispersion” of the species that appeared in the previous cycle, continues with the stage of slow evolution and closes with the appearance of new or with extinction of one of the old species. (One should not take this idea of “species creation” too literally. For example, inside a cell there could be both “fixed” and “floating” enzymes; then an evolutionary cycle could realize itself in “fixing” the floating enzymes near a previously “fixed” predecessor. Metabolism speeds up, which is good for the cell).
About Goodwin’s book. In the midst of numerous books that appear at the junction of biology, physics and mathematics, Goodwin’s “Temporal organization of the cell” is without a doubt one of the most noticeable ones. Quick and relevant response to modern advances in biochemistry, awareness of the issues in the different areas of biology, original approach to theory, critical approach to modern prejudices, broadness of the ideas considered, obvious knowledge of mathematical and physical ideas, clear precise exposition - all of these characteristics make the book enchanting for a rather wide circle of engineers, physicists, chemists, mathematicians, that are interested in biology and would like to make their contribution to the field. The ideas that are being developed in this book have the potential to become very popular.

And our goal is actually to resist this popularity.

Two main ideas that pierce Goodwin’s book are: first - oscillatory processes constitute the core of biochemistry; second - a cell is a set of nearly independent biochemical oscillators.

From our pint of view, these ideas are contradicting each other. The extent to which the first idea is correct and ingenious is the extent to which the second idea is wrong and retrogressive. Based on some of the things that Goodwin says about the idea of feedback, one can guess that psychologically this retrogression is a caused by a reaction of some of the more extreme of the “cybernetically-oriented” researchers. As a result, it seems to us that in Goodwin’s book the most advanced ideas of biochemistry collide with ramshackle mathematical apparatus. But let us get to the point.

Central idea of this book is introduction of thermodynamics that describes the behavior of the system of independent chemical oscillators. The topic in itself is rather interesting, although the author’s approach is rather narrow. Since he digresses from what is in fact the nature of the interactions between chemical oscillators, one cannot assert that equilibrium will ever be reached, and if it is, whether it could be described through one inner parameter - talandic temperature. It seems like the author is simply unaware of the existence of “different thermodynamics” that correspond to different types of interactions (assuming the same initial material - chemical oscillators).

One could have omitted this moment (after all, one should always first consider the simplest possibilities) if the author had indicated correctly the most relevant area of application of his theory.

Where and when can one really expect to find any agreement between reality and theory that is based on disregard of interactions, on the idea of independent chemical oscillators?

Probably, where there are few enzymes, and the space is great, so they do not interact or at least “don’t wait” for what may come out of these interactions.

It seems plausible that such conditions could be encountered in the original “crock-pot”, when large molecules just started appearing (let’s say, in the first billion years of biological evolution). That would be the era of “initial aggregation”.

However, Goodwin thinks that his theory is applicable to the time structure of a cell, which is highly improbable. A cell is an outcome of enormous evolution, and its organization is on the highest levels of development. All the reactions in the cell are highly specific and happen in a very specific manner; successive stages are often organized geometrically.
One should not take these statements to mean that thermodynamics of chemical oscillators is completely irrelevant when it comes to a cell. Perhaps, the following analogy is appropriate here: thermodynamics gives full solution for gases, some general understanding about large nuclei (hydrodynamic model of a nucleus is $n \approx 200$) and is completely inapplicable to the planetary system. However, it did a great job at explaining many properties of the stages of the evolutionary process that led to the appearance of the planetary system. Perhaps, “talandic” thermodynamics could play the same role in the history of cell formation. But this is just a speculation.

In conclusion we feel that it is necessary to say the following: as of right now, there is no more or less feasible possibility to create a mathematical model of a cell. One has to choose between two extreme approaches. One treats a cell as a mechanism, the other one - as a gas. As rough and crude as the first approach may be, it is infinitely closer to reality than the second approach because it stems from what is most important - the high level of evolutionary maturity of such a beautiful and complex biological object as a cell.

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