Inceptions of biomathematics from Lotka to Thom

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ABSTRACT

Mathematical biology occupies a special place at the interface between the physical, mathematical and life sciences. Is this interface merely a meeting point for dabblers venturing out of their own proper domains to work on problems of mutual interest? Or is it an incipient science in its own right, with its own particular character, principles, and practices? The past century has seen vast advances in the application of mathematical and physical ideas and techniques to biological problems, in the process transforming many of them almost beyond recognition. Nonetheless, the question of a biomathematics as a new kind of science remains open, despite several fascinating, if sometimes problematic, attempts.

Keywords: *biomathematics, history of science, thermodynamics, evolution, homeostasis, morphogenesis, catastrophe theory*

Mathematics makes invaluable contributions to numerous fields of scientific research: the intellectual discipline and the power of formal apparatus allow knowledge and insights to be uncovered that would otherwise have remained hidden and unattainable. The role of mathematics is essentially a creative one, not just allowing scientists to tie together the loose strands of the web of knowledge, but actively generating new hypotheses and lines of enquiry.

Despite these boons, the various sciences differ markedly with regard to the extend to which they avail themselves of the benefits that mathematics has to offer. On the one hand, having grown up together with mathematics[1], physics is probably as thoroughly 'mathematised' as possible or perhaps desirable[2]. Other fields are more resistant to mathematisation, attempts being tentative and problematic, and in any case often viewed with suspicion or contempt in a culture whose leading lights have thus far always managed without any knowledge of mathematics[3].

The life sciences represent an interesting intermediate case, with various disciplines and practitioners straddling the spectrum from full acceptance and integration of mathematical thought, all the way to a reluctant and grudging use of maths as a handmaiden—in our digital age of big data, no one can fully escape her clutches. To be sure, applications of mathematical ideas and techniques to problems in the life sciences predate the launch of *Science Progress* in 1916. Still, the 1910s can be regarded as a time when various strands were coalescing into a distinct subject. The past century has seen major triumphs and breakthroughs that have come to define the character of mathematical biology as a modern academic discipline, for instance in the fields of neuroscience, molecular biophysics and pattern formation, ecological interactions, the physiology of growth and metabolism, and bioinformatics, to name but a few highlights.

However, does an array of successes, no matter how successful, add up to a scientific discipline in its own right? Perhaps we have, here: a physicist who decided to make a biological entity the object of study, there: a mathematician who takes inspiration from biological situations without being overly concerned with the biological realism of every last assumption, and there again: a biologist who tries her hand at ordinary differential equations. In other words, there are enterprising physicists, mathematicians, and life scientists peeping over the interdisciplinary fences and venturing out, but without these efforts necessarily amounting to a proper science. At what point does mathematical biology acquire its own spirit, its own life, its own definite and clearly expressed physiognomy?

The question seems pertinent since some of the biggest successes (for instance in electrophysiology, biomechanics, and active matter) naturally fall within the purview of classical physics. Still, the mathematisation of biology remains to date a work in progress, and it is therefore only to be expected that the first major advances are made where the tools lie most readily at hand, and not at the 'deep end' where all is murky and unsettled.

In this historical sketch of the development of biomathematics over the past century, I will focus on the efforts of those who did jump in at the deep end. In doing so, I will barely touch upon the remarkable success stories of mathematical biology, and omit most of them altogether; for these the reader is referred to any one of several excellent textbooks[4–8]. I believe there is something of value to be found in pioneering efforts even if they were problematic or outright failures: the scientists pursuing them were driven by unique visions of what biomathematics might become, as a science with its own proper identity.

Early stirrings: the spectre of explosive population growth

The 13th-century mathematician Fibonacci (Leonardo of Pisa) introduced the series $2, 3, 5, 8, 13, 21 \ldots$ representing the number of rabbits at various points in time, starting with a single breeding pair. This 'rabbit model' was meant as a whimsical word problem couched in terms of leporids (inspired perhaps by their legendary fecundity), rather than a serious model of population dynamics[9].

Nonetheless, Fibonacci's rabbits do share with more realistically structured models a rather alarming property: that of eventual exponential growth, which will obtain whenever each individual behaves, on the average, in the same way as every other one, and can do so unfettered by resource limitations, i.e. exhaustion of nutrient supplies and space[10]; this latter assumption will never hold good indefinitely in the real world.

Several late-18th century thinkers[11,12] already recognised that exponential growth must ultimately be incompatible with the finite and limited availability of resources. Thus, an exponentially growing population will encounter harsh checks on its expansion sooner or later, for instance in the form of fierce competition and famine. Human populations are by no means exempt from such checks; whereas Condorcet imagined that enlightened reason would curb and regulate humankind's procreative impulses according to the environment's capacity for subsistence[11], Malthus was much more pessimistic in his assessment[12]. In our own day, advocates of food security frequently vaunt their ability to double (or quadruple, etc.) global food production, blithely (or

disingenuously) neglecting to mention that exponential growth at *any* positive value will catch up quickly with the most outrageously optimistic promises. Food security lies in stationarity, not in raising the ceiling at which the reckoning will come. In any case, a connection between biological phenomena and mathematical progressions had been forged.

Evolution: the quintessential theory of biology?

If one phenomenon unites all living things and, perhaps, uniquely characterises life itself, it is evolution[13,14]. Populations of biological organisms are subject to pressures that favour certain genotypes by virtue of the possessors of those genotypes converting, at a greater efficiency, a portion of their environment into more biomass associated with those 'favoured' genotypes. Furthermore, populations occasionally undergo fission, or give rise to offshoot populations that settle other areas and ecosystems. Thus, over time scales that are much longer than those of individual life histories, a development of new biological forms and functions takes place. Charles Darwin's great insight was that these selective processes alone suffice to account for the diversity we perceive in the natural world, and can help us understand how the structures and processes we encounter have come about[14].

To relate what happens at the time scales of life histories to what happens over evolutionary time is certainly a grand, deep challenge, and it is certainly not *prima facie* absurd to look upon this as a quantitative challenge, taken up with great enthusiasm by several generations of mathematical biologists since Darwin. For instance, the study of genetical systems in an evolutionary context has been much advanced by Fisher[15], Hamilton[16], and Maynard Smith[17]. Darwin presaged that much progress would come from the mathematicians, since those 'thus endowed seem to have an extra sense'[18].

If evolution is in some sense the soul of biology, its universal principle, might not the same be true of *mathematical* biology? We may find that the challenges posed by evolution call for a genuinely novel mathematical approaches, or a kind of formal thinking that is sufficiently distinct from other mathematical disciplines to emancipate biomathematics as a field in its own right. Notable developments that appear to be in such a spirit include adaptive dynamics and evolutionary invasion analysis[19,20] as well as Rice's algebra of evolution[21], itself building on Price's theorem which relates the rate of evolution to the correlation between (suitably normalised) fitness and phenotype, up to what may loosely be termed the heritability of the trait(s) considered[22,23].

An intuition common to these modern approaches is the idea that one should focus on the flow on a suitably defined manifold (phase space) as the essential mathematical structure of interest. Linking the qualitative features of this flow back to the underlying functional biology remains an open problem, whose essence is that the only thing which persists in deep time are the genes, not as molecules, but as patterns (aperiodicities) in these molecules; the rub is that the mapping from genes to fitness goes via development and involves all aspects of organismic and ecological biology. It is clearly non-trivial—worse, we do not even know what it would mean precisely to come to grips with this mapping in a generic or universal setting. Despite periodic claims and promises to the contrary (such as the recent 'systems biology' hype which is now nearing its end), the genotype-to-phenotype problem has thus far proven resistant to all

lines of attack.

Lotka's vision of a universal 'thermodynamic' law of living things

Alfred Lotka contributed to *Science Progress* in 1920, four years into its centennial existence, commenting on the explicit connection between population dynamics and evolution. He noted that both could be subsumed in a common framework, that of general dynamical systems, and that population dynamics can be recovered via a time-scale argument in which the 'evolutionary' degrees of freedom are 'frozen out'; he discusses the conditions for stability of any equilibria[24]. Ironically, Lotka is best known today for a predator-prey model in which the equilibrium is *unstable* and the system exhibits a limit cycle, which is none other than the oscillation described by Condorcet, where overpopulation leads to scarcity, which then leads to underpopulation and abundance[25]. His focus in 1920 on stable equilibria derives from the fact that local linearisation of the equilibrium point permits a Lyapunov function that may be regarded as an analogue of the thermodynamic functions which govern the dynamics of chemical systems and which endow their evolution with direction, i.e., irreversibility. At the time, such functions, which had recently been introduced by Gibbs[26] and are interrelated via Legendre transforms, serve to encode the First and Second Laws of thermodynamics and furnish criteria for spontaneity in terms of their extrema.

The idea of would-be thermodynamical potential functions for living systems was much in the air at the time, since life might either be somehow exempt from the physical and chemical laws that govern the non-living world, or its adherence to these laws might have an important bearing on how these laws were to be conceived. After all, vitalism had only recently been banished from scientific thought, and thermodynamics was still finding its feet in a world where the existence of atoms and molecules was yet to be universally accepted.

Biological exceptionalism found solace in the age-old idea of progress in evolution: the notion that living things can be arranged in a hierarchical chain of being, a *scala naturæ* which had figured as the governing principle of systematics from Aristotle onwards, to Linnaeus and Lamarck[27]. The latter injected evolution into this chain by supposing that there was an active principle, *la force qui tend sans cesse à composer l'organisation*[28]: life strives towards higher orders of organisation, or, as we might say today, towards higher complexity. If Lamarck's *pouvoir de la vie* is not to be the *vis vitalis* by any other name, it must be related to a unique property of life over evolutionary time scales. Natural selection comes to mind here. But how is evolution to be construed as an entropic force? Do such question lead us to discover the essence of mathematical biology, or are we pursuing a sterile analoguey[29]?

A crucial misunderstanding, then as now, is the perceived entropic cost of attaining higher levels of organisation. In fact, at any levels above the macro-molecular (e.g, tissue, anatomy, neural organisation), the entropic cost of biological organisation is well-nigh negligible[13,30], a point that is often ignored, possibly because of the facile metaphor of entropy as 'disorder' that dominates textbook treatments[31]. Most of the entropic cost is at the level of biopolymers and macro-molecular aggregation, and here it is paid by exchange of matter and energy with the environment. The puny additional entropic cost of organisation at higher levels is redeemed in the same way, and the

Second Law is never violated. Lotka was well aware of this, and it occurred to him that the principles of thermodynamics, whilst inviolate as far as living systems are concerned, are insufficient to derive universal dynamic laws for living systems.

If we are looking for laws that constrain the range of possibilities for such a universal 'bio-dynamics' we should look beyond classical thermodynamics: As Lotka[32] put it, *mechanism is all-important*. Perhaps this is the problem whose resolution would define the soul of mathematical biology: to characterise and exhaustively categorise these mechanisms of life, understand what unites them and develop a systematic way of accommodating their variety.

Lotka appears to have been thinking along such lines. Following Gibbs'[26] lead, he felt that something akin to a statistical treatment must be appropriate to living systems, certainly at extended scales of time and space, even if the basal units ('particles') are individual organisms rather than molecules or atoms[32]. If there is to be an analogue to statistical physics, then there should also be a counterpart to the thermodynamic limit and we could hope for the emergence (when passing to this limit) of a new law of thermodynamics, one that applies specifically to living systems. This would have to be named the Fourth Law, since Third is already taken by a law dealing with the entropy at absolute zero. Lotka's Fourth Law would have given Lamark's[28] *pouvoir de vie* a rigorous grounding, and it might even lead us to reconsider the definition of life itself, since, the Law being fundamental, if anything X is amenable to a similar statistical treatment and the passing to the limit would be subject to it, then surely X should qualify as a living system.

Lotka felt that the Fourth Law ought to concern the *flux* of energy through organisms and ecosystems. His argument was that natural selection favours efficiency with regards to the extraction of energy from the abiotic environment[33]. Thus, if total biomass stays constant (even while the species that make up this biomass are replaced by new ones), the flux of energy through that system increases. If physiological innovation leads to an expansion of the biomass that is found in a fixed unit of environment, we should again find that the total flux of energy increases through the ecosystem as a whole.

Stoichiometric constraints and homeostasis

The life sciences would look very different today—the undergraduate curriculum would be as mathematised as that of physics—had Lotka's Fourth Law made any inroads. Alas, it was not to be. One stumbling block is that energy efficiency *per se* is not necessarily or generically the quantity that is targeted by natural selection. Factors such as the raw abiotic energy supply and the available biological variability must be taken into account[33]; the simple, elegant principle crumbles in the face of myriad details which vary considerably between different evolutionary scenarios.

It is tempting to remedy the problem by recasting entropy-type arguments in terms of information. This would make sense in view of the central role played by DNA, life's repository of information. Moreover, information theory itself seems to beg for this leap, its central quantity being formally similar to statistical-physical entropy and its name being the same[34]. The essence of information is restriction of a realm of possibilities, an action that can anthropomorphically be viewed as *choosing* or *exerting*

guidance, where it is understood that these terms are to be stripped of any teleological connotations[34]. This was propounded by Guilleminot as the principle, akin to Lotka's Fourth Law, that furnishes the additional constraints left open by the First and Second Laws[35]. Wilhelm Ostwald, a dominant physical chemist of Lotka's day, observed that the problem is essentially one of stoichiometric freedoms and constraints. That is to say, we should couch the problem in terms of the various biochemical transformations that make up the organism's metabolism: these reactions each occur at a certain rate and the problem is one of reducing the freedom in the assignation of values to these rates[36]. The Second Law (which, incidentally, was misunderstood by Ostwald[37]) certainly imposes constraints on this assignation, but more is required to attain uniqueness. Ostwald believed that the organism coordinates these rates so as to 'satisfy advantageously' its energy requirements, and that this principle provides the looked-for further constraint[36].

Further progress was made by August Pütter, who observed that a subset of the rates under consideration describe exchanges with the environment; such exchanges must be mediated by a *surface* and thus the scaling relationship between biomass and surface area provides an additional constraint[38]. Pütter thus arrives at a growth curve (biomass as a function of age) that applies universally to all organisms satisfying the underlying scaling relationship; this curve is nowadays better known under the name of Ludwig von Bertalanffy[39], who promulgated a 'General Systems Theory' which built on the ideas advanced by Lotka[40].

An important, if tacit, idea in the Pütter-Bertalanffy model is that of *homeostasis*, specifically the implicit assumption (macro)chemical homeostasis with regard to the composition of the organism. Such compositional homeostasis imposes constraints on how uptake and excretion fluxes of matters are to be coordinated[41]. Organisms do maintain fairly constant ratios between the biogenic chemical elements that make up their matter, and organisms also maintain approximately constant ratios between classes of macromolecules (DNA/RNA, proteins, lipids); key metabolites in the cytoplasm and nutrients in the blood plasma are similarly maintained within certain ranges[41]. Nonetheless, a certain degree of variation is commonly tolerated, particularly as regards the accumulation of nutrient reserves. In ourselves, we can observe this as the spectrum ranging from morbid obesity to starvation, whereas in micro-organisms, reserve inclusions may constitute a substantial portion of the volume occupied by the cell[42].

Allowing for such variations, we arrive at a 'mosaic homeostasis' theory in which the organism is decomposed into a relatively small number of components, each of which is assumed to observe strict compositional homeostasis[43]. In doing so, we find that we need to supply additional constitutive relationships, which may be thought of, in unabashed anthropomorphic terms, as expressing the relative urgency with which the organism strives to restore homeostatic balance for each of these components[43]. Obversely, in the limiting case where the 'homeostatic drives' for each of these components is allowed to be arbitrarily strong, we recover the Pütter-Bertalanffy model. In any event, even the mosaic model does not uniquely specify the rates of individual biochemical transformations, but rather delimits a null space that is consistent with the various macro-chemical constraints on the fluxes.

Homeostasis and control

Bertalanffy's General Systems Theory[40] shares common ground with the 'cybernetic theory' advanced in 1948 by Norbert Wiener[44] and with modern control theory which has become an integral part of engineering[45]. From an etymological point of view, 'cybernetics' should be something like the lore of guidance and Lotka's quandary was essentially one of properly characterising this guidance. Cybernetics and control theory deal with the architecture and dynamic behaviour of *control loops*[45]. On the subcellular level, the biological correlates of these loops are second messenger signalling cascades that drive the central pathway of DNA→RNA→protein, whereas on the intercellular level, these correlates are the neuronal, paracrine, and endocrine connections between organ systems and centralised information processing stations[8].

The mathematical description of control at all levels of organisation loops has become a major activity in mathematical biology[7,8,46,47], and we may ask whether this activity is merely the fruitful application of principles developed elsewhere (e.g., control of vehicles or manufacturing processes) to similar problems in the biological arena, or whether the latter has peculiarities that set 'biocybernetics' apart.

To explore these issues further, let us consider the mammalian body as a mosaic homeostatic system, whose compositionally constant components are (i) the body such as it would be on the verge of starvation; (ii) muscle mass; (iii) glycogen stored in liver, myocytes, and the kidney; and (iv) lipids stored in adipocytes[47]. The muscle mass is tightly controlled around a value essentially governed by the mechanical demands on it (in fact the control is sufficiently tight that muscle mass and near-starvation mass are often grouped together as a single component, the *lean body mass*), whereas the lipid mass is allowed to vary over a wide range to accommodate fluctuations in the calorific content of the diet; the glycogen stores exhibit an intermediate of control tightness. In other words, the components exhibit varying degrees of tightness or slackness as regards their tendency to be restored to 'nominal' values.

A naive control engineering approach to this might be to postulate three control loops (a *myostat*, a *glycostat*, and a *lipidostat*) that guard the 'set points' of the three components. However, the (neuro-)endocrine system exerts control by adjusting the values of effector quantities such as physiological fluxes, biochemical transformations, membrane permeabilities, appetence, and the like, and many of these effectors affect multiple components simultaneously. As a result, the control loops become intertwined, and conflicting demands on the effectors can compel the system to end up in a 'frustrated' state. This phenomenon of frustrated states holds the key to understanding certain features of the system, which otherwise seem baffling, calling for a formal framework that is structured around the frustration phenomenon[48].

Another issue that sets the biological setting apart from that of engineering is an ontological one: we may observe that the muscle protein mass is more stringently controlled than the lipid reserves, but what dictates these degrees of strictness? The engineer is a conscious, forward-thinking entity, motivated by clear optimal productivity targets. The analogueous actor in the biological system is natural selection, and a satisfactory account would include selective pressures, and how these give rise to the degrees of tightness or slackness present in control loops. This is a fascinating problem: dynamical variations on a time scale typically much shorter than the organism's

lifetime induce minute fitness variations that exert their influence on the evolutionary time scale, which is much longer than the life times of individuals[13].

Growth and form: *morphē* for Lotka's *hylè*

The Pütter-Bertalanffy model is based on a biovolume/surface area scaling relationship (*Flächenregel*[49]), which means that its curve applies universally to all organisms that adhere to that volume/area relationship over the course of their growth; this turns out to be a class that includes almost all multicellular animals[41]. Outside this class, we can still follow through the argument that leads to the Pütter-Bertalanffy model as long as we can formulate *some* scaling relationship satisfied by the organism of interest as it increases in biomass. Thus we obtained a generalised Pütter-Bertalanffy theory which is virtually universal, ranging over all known kingdoms of life[41].

However, in order to derive these scaling relationships, we need to capture in formal terms how the organism acquires and changes shape over the entire course of its development. Questions of morphology (shape, geometry) are largely neglected in the line of thought predicated on thermodynamics and stoichiometry, as pursued by Lotka, Pütter, and Bertalanffy. However, there is another line of enquiry, which we can also let commence one hundred years ago (with apologies to earlier precursors), with the seminal work by D'Arcy Thompson, *On Growth and Form*[50], a science monograph that has the rare distinction of standing as a fine work of literature as well. Thompson presents many examples of how the shape and organisation of organisms are profoundly moulded by physical phenomena such as diffusion, fluid mechanics, and surface tension, combined with mechanical constraints of the genre that is more typically considered by architects and structural engineers.

Thompson appears to have been a kind of closet vitalist, regarding organisms as made up by 'vital plasma'—a generic living putty that responds to the physical forces imposed by the organism's environment. To this charming and somewhat dreamy point of view, with its distinct *fin-de-siècle* aura (similar ideas were advanced by Francé[51]), we may oppose the more positivistic idea of DNA as a *blueprint*, an all too popular metaphor in contemporary accounts, positing that morphology, physiology, and everything else is spelled out in the four-base language of the genes.

However, organisms are neither mystical putty nor edifices specified in a one-to-one manner by a molecular blueprint. In multicellular organisms, the genes specify the molecules that allow cells to communicate and determine their place and role in the development of the organism[52]. For example, biochemical gradients instruct cells to adopt certain gene expression states, or move along such gradients; the genes specify the surface receptors that bind to these diffusive factors, or that allow cells to join up in the tightly coupled sheets or bundles that form the body's epithelia, muscle cells, nervous structures and so on[52]. Thus, there is an iterative interaction between genes and biomechanics that allows the organism to develop, all the while maintaining physiological functionality during all stages throughout its development. If a simplistic slogan is required, perhaps its should be that genes work *with* the forces of physics, not *against* them.

This give and take between biological and physical drives found a crystal-clear formal specification in the work by Alan Turing on morphogenetic gradients and pattern

formation[53]. Turing built on ideas advanced earlier by Waddington[54] and Delbrück[55]. The great merit of the Turing model was that it demonstrated, by means of a concrete example, how the interaction between diffusing molecules ('straight physics') and cells responding to the local concentration of these molecules ('straight biology') gives rise to biological patterns. From a mathematical point of view, a system in which instability is driven by diffusion is remarkable because diffusion is the paradigmatic smoothing operation; this is certainly true in the realm of linear equations, but Turing's reaction-diffusion model features non-linear the cellular dynamics, supporting excitatory behaviour[56].

Stripes and spots on animal skin are the most obvious candidates for biomorphological patterns governed by a Turing-type dynamics. However, similar mechanisms may be equally important in the more fundamental patterning, such as basic ontological segmentation, the patterns of ossification in developing limbs, and the regions devoted to various processing tasks in the brain[52]. Turing's original model lacked robustness (that is to say, it is sensitive to parameter variations) as well as certain phenomena such as cell proliferation and migration; incorporation of the latter in fact removed the first shortcoming as well[57]. A remarkable achievement of the extended model is that it explains the increase in the number of stripes as the animal grows, a phenomenon observed in certain species of angelfish[57].

Although more than half a century has gone by since Turing first proposed the model, a convincing correlation between the mathematical actors and biological entities (e.g. diffusing morphogens, their receptors, and the genes encoding them) remains to be found; moreover, alternative mechano-chemical pattern generating mechanisms have been proposed[58]. In particular, local cellular behaviour both responds and contributes to the physico-chemical forces and processes to which the tissues are subjected. This interplay still remains far from being completely resolved and understood; the significance of Turing's work is that it was the first major concrete exemplar of how local biochemistry, including genetics, can work together with global physics to produce the spatio-temporal organisation that we call an organism's ontogeny or development. This is what Waddington[54] termed *epigenetics* (not to be confused with the modern sense of heritable chemical modifications of DNA).

Biomechanics on all scales of life

Besides inspiring later developments, *On Growth and Form*[50] has another important intellectual legacy, viz. that of the application of physical and mechanical principles to living systems. Structural engineering concepts such as stress, strain, Young's modulus, and so on[59], have proved to be invaluable in the understanding of the anatomical and micro-anatomical organisation of all kinds of living beings. For instance, the trunk and branches of a plant must support the leaves without buckling or breaking under wind loading, which defines minimal dimensions for a plant of a given height[60].

The mammals, as a taxonomical group, span a remarkable size range with gross overall similarity of the skeletal organisation. However, a shrew skeleton cannot simply be scaled up to give that of an elephant, as it would be far too fragile. Such disproportionalities are accounted for by scaling laws. Small and large animals share the 'intrinsic' properties of tissues, which are governed by the characteristics of molecules

and cells that are virtually the same across the taxonomic diversity. Thus, we seek a theory that accounts for differences in 'extensive' variables whilst keeping 'intensive' variables constant.

Traditionally, power laws where quantities x and y are linked by a relationship of the form $y \propto x^{\eta}$ (for some constant η) have been popular choices; and once a power law is adopted as a reasonable formula, it becomes imperative to explain the scaling exponent η in terms of the underlying physics, physiology, or biochemistry. Such *allometric regression* tends to overlook the inconvenient truths that (i) a great many monotone functions, when plotted on double-logarithmic scaled, take on an almost-linear appearance; and that (ii) allowing for the random scatter typical of a biological data sets that are routinely subjected to such analysis, we should expect that minor deviations from linearity (and often even major ones) are completely obscured. The search for η is predicated on the premise that $y \propto x^{\eta}$ is essentially correct, and this assumption is considerably weaker than generally believed. Bas Kooijman gave examples of data sets that appear to fit a straight line perfectly on a log-log plot, and nonetheless fit equally well to the graph the entirely different formula he proposed[41]. If nothing else this can serve as a reminder that even excellent agreement with the data need not imply any support for the theoretical curve that was fitted (Kooijman accordingly defends his formula on the basis of *a priori* arguments[41]).

In the example of mammalian long bones, bone dimensions have been linked to body mass via power laws, with various arguments in favour of different values for the exponents[61,62]; it quickly became clear that different groups of mammals seem to have different best-fitting exponents[63], and advanced models are based on specific details regarding the animal's stance[62]. The gains come at the cost of sacrificing what might be the main appeal of allometry, which is the idea that the posited power laws owe their universality to fundamental structural-mechanical constraints.

One of the most famous allometric laws is the named after Kleiber[64], which states that metabolic heat production scales as body mass to the power $3/4$. There are too many competing explanations to list here (their multitude should in itself negate most if not all of them); among the influential ones are McMahon's argument based on muscle diameter[61] and West *et al.*'s argument based on the branching structures of vascular trees[65], which was later disputed[66]. In any event, Dodds *et al.*[67] found the vaunted universality of Kleiber's law lacking, as different parts of the curve are better approximated by different exponents. Again: a great variety of relationships will appear only slightly curved when plotted on a double logarithmic grid, and thus one easily mistakes any such relationship for a power law.

Biomechanics has now matured into a major field, accommodating insights from fluid mechanics[68] and extending the static considerations we have discussed to locomotion and flight[69,70]. Materials science and fluid dynamics meet in the physics of the cardiovascular system, where non-linear elastic behaviour of the blood vessel walls is central to an understanding of the system's ability to respond to fluctuating loads and demands[71,72]. Moreover, striking improvements in spatiotemporal resolution in the experimental study of intracellular processes have allowed the application of structural and dynamical mechanics at the molecular scale. Active macromolecular complexes can be treated much like the girders and pulleys of macroscopic engines, and this has thrown new light on the movement of individual cells[73–75] and of chromosomes within

the cell during cell division[76,77].

The interactions between various components of macro-molecular machinery suspended in the aqueous environment of the cytoplasm give rise to new states of matter, *active polar cells*[78] in which a slew of surprising new dynamical phenomena occur[79]. These developments would appear to go beyond physicists applying the tools of their trade to problems in the life sciences: it is rather a matter of a domain of unique physical phenomena demanding the development of a novel set of tools.

Thom's general programme for biomathematics

In the broad context of Waddington's epigenetics idea, the Turing model is a proof of principle: a minimal exemplar (and all the more laudable for that). But what would be the general features of a formal theory that supports the broader context? The pedestrian approach would be to formulate the relevant dynamics as a set of differential equations, as many as it takes, and employing a supercomputer to evaluate a numerical approximation of the solution in time and space. Simulating a massive model on a supercomputer can be invaluable, provided that each of the components of the model is well-attested. Otherwise, one has merely created an inscrutable *in silico* entity that may or may not have any bearing on the original organismal system of interest. This is where these projects often fall down, occasionally not before having extracted billions of public funds in support[80]. Perhaps we can save ourselves time and effort, and moreover gain a better understanding, if we first explore the 'deep' mathematics that lies at the heart of such models, considered as a class—however vague: a prolegomena to any future Waddingtonian epigenetics theory.

This was the attitude taken in the 1960s by René Thom, a mathematician who had garnered the Fields Medal, which is the most prestigious award in the mathematical sciences, for his contributions to differential topology.[81] Thom was struck by the remarkable robustness of development: the embryo gives every appearance of a dogged determination to develop into the eventual organism, in spite of perturbations (e.g. exposure to teratological compounds). In Turing's model, the reliability of the outcome is built into the mathematical structure of the dynamics: the model exploits the randomness of diffusion, but is not beholden to it. Something like this, Thom realised, must be true of all once-and-future mathematical models of development; being a pure mathematician, he resolved to abstract this elusive *something* and study it in its own right.[82]

Thom's vision was the diametrical opposite of merely throwing off-the-shelf mathematics at a biological problem until it surrenders. He was concerned with mathematical biology as a proper *biological mathematics*. In other words, he was looking for brand new ways of mathematical thinking, both motivated by, and suited to, fundamental biological questions. Thom's focus thus chimes with the general question of what, if anything, would allow mathematical biology to stand as a distinct discipline.

If we think of cell fate, state of differentiation, and so on, as a state $\boldsymbol{x}$ and of the physico-chemical drivers (e.g., morphogen concentration in time and space) as a co-state $\boldsymbol{\mu}$, then Thom proposed that we focus on pairs $(\boldsymbol{x}_0, \boldsymbol{\mu}_0)$ where the qualitative dynamics of $\boldsymbol{x}$ changes in the neighbourhoods of the attractors of the dynamics. At such points, called *critical* or *singular* points, a slight perturbation of $\boldsymbol{\mu}$ can provoke a

qualitative change in the dynamics of $\boldsymbol{x}$, for instance, instead of tending towards $\boldsymbol{x}_0$, the state $\boldsymbol{x}$ is suddenly moving to a different attractor $\boldsymbol{x}_1$ which may very well be located nowhere near $\boldsymbol{x}_0$. This sudden, discontinuous alteration of the flow of $\boldsymbol{x}$ was termed a *catastrophe*. Away from the singular points, the system's behaviour is so uninteresting as to barely deserve much consideration: slight perturbations of $\boldsymbol{\mu}$ only lead to slight perturbations of $\boldsymbol{x}$; all is smooth and boring.

The global picture that emerges is one in which there is any number of attracting states (cell fates, etc.) which are separated by the boundaries in $(\boldsymbol{x}, \boldsymbol{\mu})$-space made up by the singularities. In keeping with this picture, Thom proposed that ontogeny (development) unfolds as a *sequence of discrete events* each of which is marked by the coordinate point $(\boldsymbol{x}, \boldsymbol{\mu})$ crossing one of these boundaries. A topological (quantitative dynamics) analysis in the close vicinity of each of these *catastrophic* events is all that is required to understand the deep structure of ontogeny.

In the neighbourhood of critical points $(\boldsymbol{x}_0, \boldsymbol{\mu}_0)$, Thom observes that the dynamics must be of a certain *canonical form*. There will obtain a generic correspondence between whatever model one may have started with and the appropriate canonical form, expressed in some convenient mathematical format. In this sense the precise formulation of the model does not matter all that much. The correspondence only holds good in the neighbourhood of the critical point, but this is not problematic since the dynamics at non-critical points is relatively unimportant. Moreover, Thom claims, given the dimension and co-dimension (i.e. the dimensions of $\boldsymbol{x}$ and $\boldsymbol{\mu}$), there is only a finite number of such canonical forms. This means that there is a definite list of cases to enumerate and work out. Once we have completed that list, we will have resolved the essential structural-dynamical features of ontogeny.

If such a research programme—an intrinsically mathematical research programme—can be completed, we will have obtained two complementary views of developmental biology: one is the global perspective afforded by the catastrophe theory as proposed by Thom, and the other is the bottom-up perspective where life scientists work to identify the genes, receptors, signalling molecule, transcription factors, and so forth that constitute the nuts and bolts of the Thomian machinery. The biologists thus appear to be relegated to a second-fiddle role in Thom's grand scheme of biomathematics, and the prospect cannot have done much to entice them to master the requisite mathematical skills[81].

Thom's proposals seem to be similar in spirit to other attempts at a deeper, more abstract biology, such as Boolean networks as a general framework for ontogeny[83]. Thom's ideas also resonate with the modern view of evolutionary dynamics, construed as a sequence of evolutionary invasion events, similarly situated at topologically privileged points of the relevant phase space[13,19,20]. In fact, Thom may well have been thinking of phylogeny as much as of ontogeny: his word for development is *morphogenèse* intended in the widest sense possible[82]. Whereas his motivating examples seem to be drawn from ontogeny and embryogenesis, his scope encompassed evolutionary dynamics as well as, ultimately, all of the natural sciences[82].

As regards the mathematical research programme he initiated, Thom himself only accomplished its goals for low-dimensional cases, and only for a severely restricted class of dynamics[81,84]. Nevertheless, the scope he set might have done for biology what Newton's *Principia* did for physics, had the programme not fallen on hard times,

in the late 1970s. Thom is thought to have provoked mathematicians with his reliance on conjecture[84] and he can hardly have done his cause much good among life scientists by claiming that only the mathematician has the right to be intelligent[85]. Sadly, the *coup de grâce* was administered by a media offensive with outlandishly fraudulent claims for the catastrophe theory[86,87]. These deplorable antics were outside of Thom's control, and catastrophe theory sank under its own hype, to be eclipsed by the advent of chaos theory[81,84], Thom's extremely worthwhile insights were lost—perhaps they may yet be recovered by a renewed interest within the life sciences in singularity theory.

Impasse or crossroads?

In broad brushstrokes, we might view the practice of mathematised natural science as tackling particular problems with bespoke formal structures, *models*, which can be seen as instantiations of *theories*. Equivalently, we may think of theories as general prescriptions for models. In addition, we seek general or fundamental principles that interconnect the theories and provide continuity between them.

Even though a scientific discipline will appear quite variegated and diverse in the day-to-day practice of the models, one may sense the presence of the underlying theories and the principles that unite them. Such a sense is prevalent in physics but conspicuously absent in biomathematics (unless one takes the view that the latter is a subsidiary of the former in any case). Is this absence to be deplored or merely a manifestation of 'physics envy'[29]? The dyed-in-the-wool pluralist would argue that all that really matters is the level of praxis, and that deeper theoretical connections are the icing on the cake. The pluralist's position is bolstered by cultural differences between the biological and mathematical sciences. Biologists tend to focus on particular systems (organisms, cells, molecules) and sometimes appear to view all of biology from the privileged vantage point of their own favourite system, whereas the mathematician seeks to strip down a problem to its bare essentials, eschewing details and resolutely throwing out all that is not relevant. Thom's provocative remarks can be seen in this light: as attempting to shock biologists into a radically different way of thinking.

But why should biologists adopt this new way of thinking, if it sits so uneasily with their prevailing working culture? Whenever we sense that seemingly unrelated problems are manifestations of the same underlying problem, we feel the urge to solve that underlying problem once and for all—such is the impetus for all mathematics. What is gained is not just the efficiency of a general solution, but also an global sense of direction. Study of the deeper theoretical structure does suggest novel hypotheses, leading to otherwise unavailable insights and knowledge. There can be little doubt that this is as true for the life sciences as for the more mathematised natural sciences. This drives the search for an essence of biomathematics; it is more than an idle intellectual exercise. The past century has witnessed the floundering of overly ambitious schemes, but promising glimmerings as well.

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