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Biology and mathematics: A fruitful merger of two cultures

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Abstract The great promise of biological science is not its 'mathematization' per se, but the creative interaction between experimental biology and what one, in analogy to physics, may simply call theoretical biology. The key to, and also the great challenge in, fulfilling this promise is to find the correct fundamental notions to mathematically describe biological reality.

The previous century was apparently that of physics, whereas the new one is supposed to become the century of biology. Why is this? In a thought-provoking paper Evelyn Fox-Keller (2007) argued that, although math might be quite useful, biology is effectively too complex to allow mathematics to pervade its analytic apparatus. I will argue that a historically more careful and fundamental analysis points to the opposite, viz., an extremely fruitful merger explaining the successes of biology to come.

Why is it that we may expect our gain on biological insights to accelerate? To answer this question some feedback from the history of physics, which Fox-Keller associates with "all encompassing laws", may be helpful. First of all, wherever we look, it took physics lots of time to arrive at what we now call physical laws. Particularly mechanics as the first typical representative of present-day physics needed centuries (Dijksterhuis 1969) to discover that mathematics is the only appropriate language to quantify "physical" phenomena and that it *first* had to isolate the relevant *fundamental* notions before arriving at a mathematical description that "fits". This does not sound consequential but it is. Here is an example.

Newton's second law asserts that the time derivative of a particle's momentum equals the force exerted on it ($\boldsymbol{F} = \mathrm{d}\boldsymbol{p}/\mathrm{d}t$). Did you spontaneously realize that momentum ($\boldsymbol{p} = m\boldsymbol{v}$) as the product of mass and velocity, a vector quantity with size (m/s) and direction in space, is the right way of doing it? Most probably not. At least it took physics centuries to arrive at this elegant mathematical simplification of our everyday experience. Furthermore, has one ever derived Newton's law? The answer is a clear *no*. It just turns out to be the right *mathematical* way of formulating things, and someone has to find it. Newton did. As always in science, the key to success is asking the right questions (Dijksterhuis 1969). Here, we first need the right notion, viz., momentum, entailing a quantitative formulation and we then have to find the "law" governing it. This takes time, often considerable time, but once found, progress can be explosively quick and penetrating. We will soon come to a suggestion why.

The thesis of Fox-Keller (2007) that physics has all-encompassing laws is wrong. Each law refers to a specific domain of validity, so-to-speak a 'universality class' depending on for instance the scale in space (meters, mm,

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We are initiating a new series of short communications in *Biological Cybernetics*, called *BC Forum*; here is the first contribution.
A submission can be commentary-like but should ideally also develop an interesting new idea for the general neuroscience community. The Editor and Coeditors-in-Chief realize that 'new' is open to interpretation by our readers, so even occasional polemics will be welcomed here, provided the arguments are clear. Also welcomed in the BC Forum are novel theoretical demonstrations to support classical results or innovative mathematical proofs of known results. In short, *BC Forum* will be a platform for short provocative commentaries and new, concise theoretical/mathematical demonstrations. In general, their length should not exceed two BC pages. We hope you will enjoy them!

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μm, nm,...) and time (s, ms, μs, ns,...) at which we look. Furthermore, *universality* is a notion that only applies to the *mathematical* formulation of physical reality and not to the reality as amenable to experiment itself. The latter may each time look quite different but mathematics then unifies all these different phenomena into one grand, unifying concept.

Wiener (1948) was one of the first to observe the unsurpassed possibilities that mathematics can offer to biology: it is *only* mathematics that allows a quantitative formulation of what is going on in biology, as it does in physics. In view of the richness of mathematical techniques meanwhile available, the mathematization of biology is now a strongly evolving, and flowering, challenge. Mathematics being at hand at every scientific corner, the realization that biology and mathematics belong together is occurring incomparably faster than in physics, although it may nevertheless take a while to find the right fundamental notions.

The point is not that all biologists must acquire a deep mastery of mathematics but simply that a communicative literacy in and appreciation for the power of mathematical formulation benefits all who work at the interface between descriptive and analytical sciences, that is, nearly all biologists. As a consequence, the highly profitable interrelationship between biology and mathematics is readily discovered.

When we consider why physics was so successful, we can learn from its rich experience over the centuries (Dijksterhuis 1969): a theory need not be based on experimentally verified facts alone but can also reveal, which may for the moment mean hypothesize, mathematical principles that lead to a consistent explanation of experiments. That is, it should have *predictive* value so that part of a theory may well be *prae facto* instead of *post factum* and, hence, *invite* experimental verification. It was exactly this constructive interchange between theory and experiment that (arguably) made physics the hallmark enterprise of the twentieth century. Who could argue that a similar history is not in store for essentially all of biology that aims at a quantitative description of the natural world?

Do, then, "universal" laws exist as "universally" valid mathematical descriptions of biological reality? Let me give three examples from neurobiology showing that on a suitable scale in space and time universal laws do exist. First, our scale is the neuronal and not the ion-channel one and we focus on a neuron as a *threshold* element, meaning that it can produce an action potential only if its membrane potential exceeds a threshold. This notion has turned out to be extremely fruitful. Not only did it lead to formal or McCulloch–Pitts (1943) neurons that work by discretizing time into 1ms time bits and inputting either a 1 for active, meaning spike emission, or 0 for the inactive state but also to Hodgkin and Huxley (1952), whose work earned them the Nobel prize and initiated an overwhelming plethora of highly detailed neuron models describing many different situations but all effectively exhibiting a threshold.

Learning in general happens at synapses in the context of neuronal dynamics. *Spike-timing dependent* plasticity (or STDP) has appeared as a universal mechanism to explain synaptic learning. Its key idea (Gerstner et al. 1996; Markram et al. 1997) is the *learning window*. For an excitatory synapse this means that, if the postsynaptic neuron fires and the presynaptic spike arrives slightly earlier, then the synapse is doing its job, and depending on the difference in time between the occurrence of the two spikes is more, or less, strengthened. If on the other hand the presynaptic spike comes "too late", i.e., after the postsynaptic neuron has fired, it is to be weakened. The essential ingredient is the learning window as a *function* describing increase or decrease of synaptic efficacy in dependence upon the arrival times of pre- and postsynaptic spikes. The only thing that changes from one case, e.g., type of synapse or brain area or species, to the next is the learning window. A huge quantity of experimental evidence has meanwhile shown the striking fruitfulness of this idea.

Finally, we turn to a third notion underlining the existence of universality in neurobiology. It is population vector coding (Georgopoulos et al. 1986) as a mechanism for explaining how populations of motor cortex neurons encode movement direction. One may well call this "Newton's second law for motor neurons". As with Newton's law it is an experimental fact, based on the mathematical notion of vector. One assigns to each motor neuron a preferred direction, a unit vector. Then the resulting motion encoded by the neuronal population is the vector sum of the preferred directions of the individual neurons multiplied by their firing rate. The predictive power of this rule is formidable, as is its utility to computational modeling, i.e., "theoretical" neuroscience.

In short, on the basis of the history of physics and a proper interpretation of the way in which mathematics is used to quantify natural phenomena one may well expect an often detailed, quantitative explanation of biological reality; that is, of those parts of biology that are amenable to a quantitative description. The great promise of the future is not the 'mathematization' of biology as such but the creative *interaction* between experimental biology and what one, in analogy to physics, may simply call theoretical biology. The history of science tells us that precisely this is the key to success, viz., finding the right fundamental notions, mathematically formulating their 'universal' laws, and specifying their range of validity in space and time. Not more and not less. Having predictive value they invite new experiments to challenge their validity.

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