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Universality, complexity and the praxis of biology: Two case studies

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ABSTRACT

The phenomenon of biology provides a prime example for a naturally occurring complex system. The approach to this complexity reflects the tension between a reductionist, reverse-engineering stance, and more abstract, systemic ones. Both of us are reductionists, but our observations challenge reductionism, at least the naive version of it. Here we describe the challenge, focusing on two universal characteristics of biological complexity: two-way microscopic–macroscopic degeneracy, and lack of time scale separation within and between levels of organization. These two features and their consequences for the praxis of experimental biology, reflect inherent difficulties in separating the dynamics of any given level of organization from the coupled dynamics of all other levels, including the environment within which the system is embedded. Where these difficulties are not deeply acknowledged, the impacts of fallacies that are inherent to naive reductionism are significant. In an era where technology enables experimental high-resolution access to numerous observables, the challenge faced by the mature reductionist—identification of *relevant* microscopic variables—becomes more demanding than ever. The demonstrations provided here are taken from two very different biological realizations: populations of microorganisms and populations of neurons, thus making the lesson potentially general.

It is not an everyday experience for a scientist to expose his or her ideas to analyses by a group of professional philosophers of science. While undeniably honoring, succumbing one's cogitative habits to predacious philosophers of science takes a fair amount of courage; even more so as both of us consider ourselves romantic scientists for whom words and metaphors are means to convey a message, to communicate with the understanding that things might, should and probably are misrepresented, misused, and thus become a bed for further fertilization of new ideas. In Konstanz we attempted to initiate a discussion by painting an integrated picture, where biology is described as complex natural phenomena at the population level, rather than as a complicated programmed multi-agent engineered system that is designed to accomplish pre-defined functions. We presented detailed experiments on two very different biological systems—populations of microorganisms and populations of neurons—that expose aspects of universality in biological systems. These involve universal fluctuations, emergence of statistical similarity in the temporal dynamics of, as well as in the crosstalk between levels of organization, invariance over extended ranges of time scales, and non-uniqueness of macroscopic–microscopic relations. We argued that as such, biology resists naive reductionism (or its current expression in terms of reverse engineering, discussed below) as means to achieve what is expected from a scientific discipline, that is—exposing causal relations. Of course we acknowledged that naive reductive procedures might prove efficient as practical means to advance controlling of biological phenomena, a desired biomedical outcome; this, however, is technology—not the kind of science we wanted to discuss in Konstanz.

The *microorganism system* (Stolovicki, Dror, Brenner, & Braun, 2006) is a genetically mutated population of yeast cells,

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confronted with a novel challenge they had not encountered along their history in evolution. Specifically, a strain of the yeast *Saccharomyces cerevisiae* was engineered to recruit the gene *HIS3*, encoding an essential enzyme from the histidine biosynthesis pathway, to the GAL regulatory system, responsible for galactose utilization. The GAL system is known to be strongly repressed when the cells are exposed to glucose. Therefore, upon switching to a medium containing glucose and lacking histidine, the GAL system and (with it) HIS3 are highly repressed, and the cells encounter a severe challenge. Thus we ended up with a population of yeast cells that, in order to survive, *must* find a way to develop novel modes, rewiring its complex network of interactions between different levels of organization—environment, cell physiology and genome. It turns out that such yeast systems converge to a solution by exploration; in fact, the rewired cells adapted to the challenging environment within a surprisingly short timescale, seemingly breaking an efficacy barrier that is dictated by the dimensionality of the problem (see below). Moreover, each cell in the population had the potential to find a solution and the adapted state was stably inherited along generations. We have shown that this adaptation presents an evolutionary route that is complementary to random mutations and selection. This experimental approach made it possible for us to measure long-term intracellular processes underlying the exploratory dynamics, manifested by global non-specific and non-reproducible gene expression responses of the adapting populations.[1]

The *neural experimental system* (reviewed in Marom & Shahaf, 2002; Morin, Takamura, & Tamiya, 2005) is a large scale randomly connected network of neurons, developing *ex-vivo* on top of a substrate-embedded multi-electrode array. *Ex-vivo* developing cortical networks are composed of cells obtained from cortices of embryonic or early postnatal animals, usually rats. The preference for early stage cells is due to the fact that the later in development cells are harvested, the less probable it is that they will survive and adapt to a new environment. Immediately following their extraction from the cortex, most of the neurons have no axo-dentritic extensions and are disconnected from each other. A typical cortical network, developing in a 20-mm diameter plate, may contain up to 100,000 neurons. The neurons begin to extend their axons and dendrites within hours after plating, proceeding from a population of unconnected individual cells, independent from each other structurally, to a densely connected mature phase. At this mature phase, the network is topologically complex, showing immense number of functional synapses and broadly distributed connectivity. The network contains all the types of cells that are present in the cortex at the time of extraction, including glial cells. The substrate embedded electrode array on top of which the neurons evolve, enables monitoring and stimulation of network points at high spatial and temporal resolution over a wide range of scales. This reduced set up demonstrates the wealth of possible instantiations of two primitives that characterize neural systems: (i) an extensive functional connectivity that enables a large repertoire of possible responses to stimuli; and (ii) sensitivity of the functional connectivity to activity, allowing for selection of adaptive responses. Over the past 15 years a set of tools was developed, enabling access to many fundamental issues that concern the activity of neurons in their networks. These include studies of morphological constraints, dynamics (spontaneous and evoked) of neuronal thresholds and synaptic connections at the cellular and population levels, relations between cellular and network levels of organization, representation of environmental input as a population phenomenon, adaptation and learning.[2]

The fact that the two systems—yeasts and neurons—are very different in their physics of coupling mechanisms, makes the interpretation of the foregoing universal features potentially relevant to the discussion of biology in general.

Our approach to these systems is based on the acknowledgment that both are instantiations of populations of weakly and dynamically-coupled elements (genes and neurons). Much of present-day understanding of population dynamics in general, and of microorganism and neural populations in particular, relies on sub-cellular and single cell data. The macroscopic dynamics as well as function are described as the integrated outcome of underlying, microscopic cellular complexity. Clear distinctions are made between the source of variability and the process of selection applied by the environment; in any given environment, individuals with higher functional capacity are selected. The concept of scale separation is fundamental to this picture. In the cases discussed here, time scale separation is assumed to exist between the fast microscopic dynamics and the slow macroscopic, adaptive, environmentally affected functionality. This scale separation is the major justification used for the routine practice of integration over microscopic degrees of freedom. Such coarse-graining enables to connect microscopic configurations with the macroscopic complex dynamics.

Notwithstanding the success of the above approach, it is challenged by observations that might require reconsideration of its basic assumptions: (1) Practically identical microscopic configurations may give rise to seemingly different macroscopic dynamics and function; (2) there is no time scale separation between levels of organization; and, (3) the coupling to environmental dynamics cannot be treated as a mere filtering effect. In the microorganism system, the above features are manifested in identical genomes that can exhibit quite different macroscopic phenotypes; this phenotypic variability becomes especially significant in isogenic cell populations within diverse biological contexts. Phenotypic variation is generated by a multitude of physiological mechanisms and can be maintained by epigenetic inheritance with variable degree of fidelity. Genetic and phenotypic variations generally coexist in a population, and the connection between them is complex and not one-to-one. In neural systems, the relation between cellular or network configurations to macroscopic, adaptive function, is not unique nor specific: the same neurons, networks or even the same pattern of activity, may be mapped to seemingly different functions. Moreover, the traditional allocation of slow dynamics to extended neural configurations, and the fast dynamics to the spatially microscopic configuration, does not hold. All levels

[1] For a recent review see Braun (2015).

[2] See, for instance, Branch, Wheeler, Brewer, & Leckband (2000), Chang, Brewer, & Wheeler (2001), Segev, Shapira, Benveniste, & Ben-Jacob (2001), Shahaf & Marom (2001), DeMarse, Wagenaar, Blau, & Potter (2001), Tal, Jacobson, Lyakhov, & Marom (2001), Segev et al. (2002), Marom & Shahaf (2002), Shefi, Golding, Segev, Ben-Jacob, & Ayali (2002), Xia, Gopal, & Gross (2003), Eytan, Brenner, & Marom (2003), Eytan, Minerbi, Ziv, & Marom (2004), Wagenaar, Pine, & Potter (2004), Marom & Eytan (2005), Bonifazi, Ruaro, & Torre (2005), Wagenaar, Madhavan, Pine, & Potter (2005), Tateno, Jimbo, & Robinson (2005a, 2005b), Wagenaar, Pine, & Potter (2006), Eytan & Marom (2006), Novellino et al. (2007), Baruchi & Ben-Jacob (2007), Chiappalone, Vato, Berdondini, Koudelka-Hep, & Martinoia (2007), Pasquale, Massobrio, Bologna, Chiappalone, & Martinoia (2008), Ham, Bettencourt, McDaniel, & Gross (2008), Eckmann, Jacobi, Marom, Moses, & Zbinden (2008), Shahaf et al. (2008), Wallach, Eytan, Marom, & Meir (2008), Marom et al. (2009), Minerbi et al. (2009), Zrenner, Eytan, Wallach, Thier, & Marom (2010), le Feber et al. (2010), Kermany et al. (2010), Wallach, Eytan, Gal, Zrenner, & Marom (2011), Kanter et al. (2011), Wallach & Marom (2012), Weihberger, Okujeni, Mikkonen, & Egert (2013), Reinartz, Biro, Gal, Giugliano, & Marom (2014) and Keren & Marom (2014).