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BACK TO THE BASICS: THE DYNAMIC OF INFECTIOUS DISEASES IN CONTEXT

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ABSTRACT

The epidemiology of infectious diseases shares with theoretical and empirical ecology the integrated analysis of the dynamics of different populations of host-pathogens or preys-predators-parasites in context, i.e. as part of a vast web of interactions, webs with the double character of matter/energy transfer and differential reproductive success. Such dynamics mutually influence each other, but do not map one into each other. After the 1950 and especially after the 1990s, such analyses have been integrated to the analyses of phenomena taking place at the micro-level, including the dynamics of genomic and post-genomic structures and networks. As discussed at length in the present paper, reductionist perspectives in the fields of both molecular and evolutionary biology were instrumental to the progress of such disciplines in the 1960s and have contributed to the understanding of many simple phenomena. Notwithstanding, major progress had taken place in the fields of molecular biology, biomathematics and computation, making such oversimplified models not only misleading in terms of a proper understanding of biology, but detrimental to the assessment and analysis of complex phenomena, such as the dynamics of cancer or the emergence and transmission of resistant strains in environments under anthropic pressure. Alternative views do exist, at least since the late 1980s, as advanced by authors such as David Hull and, more recently, Eva Jablonka and coworkers, among others, and should be fully explored in order to move beyond the strictly gene-centered paradigm. The so-called "beans bag genetics" is not only no longer necessary, but has been hindering the progress of evolutionary biology, epidemiology and molecular biology itself. Despite the enormous popularity of such oversimplified perspectives among the lay audience, those working in the forefront of biology should try to be as precise in their empirical work as sound in the use of concepts and design of comprehensive research programs.
Keywords: Ecology; infectious diseases epidemiology; philosophy of biology; molecular biology.

RESUMO

DE VOLTA AOS FUNDAMENTOS: A DINÂMICA DAS DOENÇAS INFECCIOSAS NO SEU CONTEXTO. A epidemiologia das doenças infecciosas compartilha com a ecologia teórica e empírica a análise integrada da dinâmica de diferentes populações de hospedeiros-patógenos ou presas-predadores-parasitas em contexto, ou seja, como parte de uma vasta rede de interações, redes estas com a dupla natureza de transferência de matéria/energia e sucesso reprodutivo diferencial. Estas dinâmicas se influenciam mutuamente, mas não podem ser automaticamente superpostas uma à outra. A partir da década de 1950, e, especialmente, a partir dos anos 1990, essas análises vêm sendo integradas a análises de fenômenos que têm lugar em um nível micro, o que inclui as dinâmicas das estruturas e redes genômicas e pós-genômicas. Com discutido em detalhe no presente artigo, as perspectivas reducionistas tanto no campo da biologia molecular, como da biologia evolucionista foram instrumentais para o progresso dessas disciplinas na década de 1960 e contribuíram para a adequada compreensão de uma série de fenômenos simples. Contudo, progressos notáveis têm sido feitos no âmbito da biologia molecular, biomatemática e computação, o que faz desses modelos hipersimplificados

não apenas falsos em termos de uma compreensão acurada da biologia, mas prejudiciais à avaliação e análise de fenômenos complexos, como a dinâmica do câncer ou a emergência e transmissão de cepas resistentes em ambientes sob pressão antrópica. Visões alternativas existem, ao menos desde o final da década de 1980, como nas propostas de autores como David Hull, e, mais recentemente, de Eva Jablonka e seus colaboradores, entre outros, e devem ser exploradas em detalhe de movo a avançarmos para além do paradigma exclusivamente centrado nos genes. A assim denominada "genética do saco de feijões", não apenas é hoje desnecessária, como vem funcionando como um obstáculo ao progresso da biologia evolucionista, epidemiologia e da própria biologia molecular. A despeito da enorme popularidade dessas perspectivas simplistas entre o público leigo, aqueles que trabalham na vanguarda da biologia deveriam tentar ser tão precisos em seu trabalho empírico, como consistentes no uso de conceitos e na formulação de programas abrangentes de pesquisa.
Palavras-chave: Ecologia; epidemiologia das doenças infecciosas; filosofia da biologia; biologia molecular.

RESUMEN

DE VUELTA A LO BASICO: EL CONTEXTO DE LA DINÁMICA DE LAS ENFERMEDADES INFECCIOSAS. La epidemiología de las enfermedades infecciosas comparte con la ecología teórica y empírica el análisis integrado de la dinámica de distintas poblaciones hospedero-patógeno o depredador-presa-parásito en contexto, es decir, como parte de una amplia red de interacciones, redes con el doble carácter de transferencia de materia-energía y éxito reproductivo diferencial. Estas dinámicas se influencian mutuamente, pero no pueden ser automáticamente superpuestas, una dentro de la otra. A partir de la década de 1950 y especialmente después de los años 1990, estos análisis se integraron al análisis de fenómenos a nivel micro, lo que incluye la dinámica de estructuras de redes genómicas y postgenomicas. Como se discute en detalle en el presente trabajo, las perspectivas reduccionistas en el campo de la biología molecular y evolutiva fueron instrumentos para el progreso de las mismas en los años 1960, y contribuyeron a la adecuada comprensión de una serie de fenómenos simples. A pesar de esto, los mayores progresos ocurrieron en el campo de la biología molecular, la biomatemáticas y la computación, realizando modelos sobresimplificados, perdiendo no solamente en términos de una adecuada comprensión de la biología sino también en detrimento de la evaluación y análisis de estructuras complejas, tales como la dinámica del cáncer o la emergencia y transmisión de cepas resistentes en ambientes bajo presiones antrópicas. Existen visiones alternativas, al menos desde los años 1980, desarrolladas por autores tales como David Hull y, recientemente Eva Jablonka y co-autores, entre otros, y debe ser explorado para ir más allá del estricto paradigma centrado en los genes. La llamada "genética de la bolsa de frijoles" no solo es innecesaria sino que ha escondido el progreso de la biología evolutiva, epidemiología y biología molecular misma. A pesar de la gran popularidad de tales perspectivas sobresimplificadas entre la audiencia lego, aquellos que trabajan en la vanguardia de la biología deberían intentar ser tan precisos en su trabajo empírico como consistentes en el uso de conceptos y diseños de programas de investigación exhaustivos.
Palabras clave: Ecología; enfermedades infecciosas; epidemiología; filosofía de la biología; biología molecular.

INTRODUCTION

Theoretical ecology and the modeling of infectious diseases have a common origin and fate. Some of the leading figures working in both fields, since the pioneer work of Alfred Lotka (1880-1949) and Vito Volterra (1860-1940) have worked in the intersection of such mutually reinforcing disciplines. Leading contemporary authors such as Robert May (1936-) have major contributions to both. Many of May's fundamental works should be properly classified as belonging to the interface of such disciplines. Originally trained as a physicist, in Australia, May moved to the UK where he published a series of fundamental papers and books with either a focus on theoretical ecology (May 2001 [original edition from

1972]) or the epidemiology of infectious diseases (Anderson & May 1992) that could be rather viewed as a comprehensive, single corpus of knowledge.

Profiting from such initial developments, the dynamics of infectious diseases has been analyzed since then in the context of the advances taking place at the macro-level (the web of interactions as defined by ecology), but progressively integrated with the fundamental insights from the phenomena taking place at the micro-level. After the discovery of the double helix of DNA in the early 1950s, the field of molecular biology experienced a boom that became even more vigorous after the 1990s, with the fast progress of both molecular methods and techniques as well as computational biology and applied mathematics. Such developments define a new paradigm: genomics, i.e. the comprehensive study of the genetic structure of whole organisms.

In recent years, there have been many attempts to fully integrate analyses carried out at the micro-, meso- and macro-level, such as in the analysis of huge datasets containing information relative to the genetic structure of individuals, their meso-level characteristics such as clinical or behavioral data, and the context (social and environmental) in which they are inserted/interact with. Such multi-level analyses remain a challenge from the point of view of concepts, methods and tools, but notwithstanding represent the winding road to be traveled in the near future by experts in different fields such as genetics, epidemiology, and a variety of clinical specialties, from infectious diseases to oncology (Hernandez & Blazer 2006).

On the other hand, some recent developments in the field of evolutionary biology have compromised the understanding of phenomena taking place at both the micro- and macro-levels, driving concepts and analyses toward a reductionist perspective in the context of which organisms are reduced to passive entities ('vehicles', following Richard Dawkins' terminology). According to such perspective, the complex interactions between micro-organisms, plants, animals, as well as the abiotic factors, such as the weather and the physical and chemical properties of soils and waters, have been viewed under the label of 'extended phenotypes' (again, using concepts originally coined by Richard Dawkins). One could say that such unfortunate terminology, inaugurated by the oxymoron 'the selfish gene' (the most unfortunate of all such concepts, due to a misleading combination of anthropomorphism ─ genes can be everything, but "selfish", and bad molecular biology ─ a discipline which very stuff is made of dynamic interactions, then everything but composed by 'selfish' units; anthropomorphisms apart), is just irrelevant. But, as discussed in this text, it seems not to be the case, at least respecting the epidemiology of infectious diseases.

A typical illustration of such misguided understanding of ecology can be found in the legend of plate 7 of Dawkins' book *The Ancestor's Tale,* where a picture of an European beaver (*Castor fiber*) is described as "[a beaver] swimming in its extended phenotype" (verbatim) (Dawkins 2004, Appendix: Plates, Plate Nº 7).

Such misconceptions have been received with both anger and applause by geneticists, evolutionary biologists, epidemiologists, and mathematical modelers. Those who criticize them ─ like myself ─ are concerned with throwing away the baby with the bath water. On the other hand, those with a sound background in biology who use such terminology usually argue that simple concepts are both proxies of real phenomena and tools to inform mathematical modeling and statistical analyses.

The perspective adopted in the current text is deliberately personal, despite its debts to different authors, such as David Hull and Niles Eldredge. My main aim is to foster debate, paving the way for a comprehensive understanding of contemporary biology, incorporating insights and empirical findings from different disciplines, from molecular biology to ecology. Of course, people who think biology can be properly understood on the basis of 'downward causation' would rather view such debate as a waste of time, or even worse, as a way to make things more confusing (see a former contribution on the same issues in Bastos 2009).

As discussed in this text, the working concept of 'genes', as originally coined by Williams ("any hereditary information for which there is a favorable or unfavorable selection bias equal to several or many times its rate of endogenous change") (Williams 1966, p. 25), and later reworked by Dawkins in his concept of 'replicators' is viewed as not only unnecessarily simplistic in the light of contemporary molecular

biology, but no longer useful for the purposes of contemporary epidemiology.

From the perspective of molecular biology, no one criticized such 'working definition' of genes in more acid terms than Stent (cited by Hull 1988):

"This perverse definition [in terms of selection] denatures the meaningful and well-established concept of genetics into a fuzzy and heuristically useless notion" (Stent 1977, p. 34, Hull 1988, p. 408).

In the present text, Stent's sentence will be discussed from a double perspective: a) the idea that a selection-oriented gene, later redefined as a 'selfish gene' (which adds to Williams' original definition a new flavor of inaccuracy), is confusing from the perspective of molecular biology, and b) the insight such concept is not only "[a] heuristically useless notion" (Stent 1977, p. 34, Hull 1988, p. 408), but rather corresponds to a conceptual obstacle to be challenged for the sake of the soundness and consistence of contemporary epidemiology.

Swamped in such conceptual muddle waters, which became very popular among non-experts in recent years, the epidemiology of infectious diseases is forced to move back to the basics. The basics, in this sense, mean to re-frame the concepts and empirical findings of epidemiology in the broad context of ecology as a web of interactions, a web beyond the world of selfish monads. Such selfish monads seem to be a contemporary reenactment of Leibniz's atomistic world.

A mere replacement of the concept of monad, as originally formulated by Leibniz, by the concept of 'selfish gene', as coined by Dawkins, in the text as follows speaks by itself.

However, it would be unfair to Dawkins's concepts to deny one fundamental difference between his concepts and Leibiniz's understanding of monads: the world of selfish genes was stripped of one of the key dimensions of Leibniz's world view ─ God!, called by him: "The supreme monad… the doer of the pre-existing harmony". In this sense, Dennet's reasoning is right ─ such new world view challenges Aristotle's "Prime Mover, the for-which to end all for-whiches" (Dennet 1995, p. 24). Notwithstanding, from my point of view, such God-free world view remains as atomistic as the original one:

"Monads are to the metaphysical realm what atoms are to the physical/phenomenal. Monads are the ultimate elements of the universe. The monads are 'substantial forms of being' with the following properties: they are eternal, indecomposable, individual, subject to their own laws, un-interacting, and each reflecting the entire universe in a pre-established harmony […]. Monads are centers of force; substance is force, while space, matter, and motion are merely phenomenal.

The ontological essence of a monad is its irreducible simplicity. Unlike atoms, monads possess no material or spatial character. They also differ from atoms by their complete mutual independence, so that interactions among monads are only apparent. Instead, by virtue of the principle of pre-established harmony, each monad follows a preprogrammed set of 'instructions' peculiar to itself, so that a monad 'knows' what to do at each moment. (These 'instructions' may be seen as analogs of the scientific laws governing subatomic particles.)" (available at http://en.wikipedia.org/wiki/Leibniz).

So, if one wants to salvage the original vitality of infectious diseases epidemiology and pave the way for the future, it's time to move back to the basics. To move back in order to move forward, cautiously but firmly, challenging misconceptions, towards a better understanding of the dynamics of infectious diseases in context. That's a long way ahead ─ a debate this essay aims to stimulate.

GENES ARE NOT ONLY REPLICATORS, BUT REPLICATORS AND INTERACTORS

Conceptual accuracy is many times relegated to secondary role by those working in the field or in the bench, partially as a consequence of an overburdened routine of fieldwork and/or laboratory investigation. But, as can be easily perceived (independently of any epistemological reasoning) by anyone carrying out his or her routine work, there is not such a thing called 'raw empirical findings'. One does not go to the field or to the lab to look for empirical facts in a purely haphazard way. The very structure and logistics of field surveys or the technical devices and methods one chooses to use in the assessment of a given problem show science inevitably follows Goethe's famous dictum: "What man knows, man sees" (Goethe, see http://www.fact- archive.com/quotes/Johann_Wolfgang_von_Goethe). My own experience

with naïve students that many times answered my question about their analytic plan, quipping: "I will cross-compare everything (i.e. all variables) with everything", documents they would not only violate the so-called Hill's criteria of causation (see, for instance, http://www.drabruzzi.com/hills_criteria_of_causation.htm), but the very logic of biostatistics. Such logic corresponds to 'taming the chance' (in the fortunate expression coined by Ian Hacking), not to be enslaved by it (i.e. not to be the hostage of a myriad of conceptually implausible chance associations).

In this sense, to consider 'genes' (even as an operational definition) as just 'replicators' is misleading both in terms of molecular and evolutionary biology. As thoroughly discussed by Hull (1988, 2001), genes are simultaneously 'replicators' and 'interactors'. Recent empirical findings confirm and extend Hull's original insights, forged in the late 1980s.

Recent analyses have addressed the complex interactions between genes and genes, genes and proteins, and genes and many other molecules and structures deeply immersed in the cell architecture. Contemporary biology has called attention to different epigenetic phenomena, such as DNA methylation, the role of histones in the replication of DNA, and RNA interference (RNAi). Such epigenetic phenomena may alter gene expression in a substantial extent, either as discrete modulating factors, but much probably in a concerted, interactive, way (as loops and/or complex networks of multiple elements) (Simons 2009).

In the context of the gene-centered paradigm informed by selfish genes, 'development' (i.e. the genotype-phenotype unidirectional route) is the only causal link between what is called 'replicators' (the genes) and 'vehicles' (i.e. organisms), but such paradigm severs the other, non-developmental, causal links between genes, cells and organisms, such as the complex interactions between DNA, the chromosome structure and the cell environment where such structures and elements are immersed (Hull 1988, 2001, Jablonka & Lamb 2006). The actual biological structure involved in the genesis of variation and which is the target of selection is a complex mix of genetic, epigenetic and organismic (and even supra-organismic) elements and structures (as discussed in the next sections), instead of a hypothetical naked DNA structure housing simple, discrete selection units disposed as beads on a line. Such oversimplification of the real dimension of molecular biology as a putative basis of population genetics was nicknamed by Ernst Mayr 'beans bag genetics' (Mayr 1988).

The so-called 'beans bag genetics' did not emerge and thrive in a vacuum, but rather corresponded to a genetic paradigm informing a comprehensive 'research program', in the sense the Hungarian philosopher of science Imre Lakatos understood such expression, i.e. "a succession of slightly different theories and experimental techniques developed over time, that share some common idea, considered by Lakatos their 'hard core'" (Lakatos 1978, see http://en.wikipedia.org/wiki/Imre_Lakatos). Such research program remained a 'progressive research program' (again following Lakatos' terminology) for decades, but, more recently, with the major advances in the fields of molecular biology, computation, mathematics and statistics, it does no longer make sense, and may inform rather a 'degenerating research program' (once again, following Lakatos' original formulations).

The complexity of real-world genetics and the pressing need to simplify it in the early 1950s as a proxy for the then emerging population genetics and biostatistics is summarized by Hull: "Right from the start, Fisher, Haldane, and Wright realized that genes interact, and they included in their earliest works ways of treating such interactions. Wright for one was especially interested in physiological genetics, however these discussions were among the most difficult in their writings as well as being among the most inconclusive. All in all, it is truly amazing how much progress could be made in understanding both the local transmission of characters and short-term evolutionary changes by treating genes as if they were independent, isolated particles ─ beans in a bag" (Hull 1988, p. 66).

Of course, this does not mean that the formidable progress taking place in the period such classic authors carried out their analyses should continue for ever and ever, without a call for a deep reworking of the classic paradigm.

The history of contemporary epidemiology witnesses both the grandeur of past achievements and the limitations of the methods used to explore problems that proved to be more complex and subtle than the ones addressed by its founding fathers. The call for new paradigms has been discussed at length

by books (Johnson 2006) and papers which explore in detail the prospects for epidemiology in the near future (Susser & Susser 1996a, 1996b).

ORGANISMS ARE NOT PASSIVE VEHICLES BUT FULL INTERACTORS

"Entities other than single genes interact with their environments so that the resulting replication is differential. Without replication there would be no evolution at all, but without differential replication evolution would not amount too much." (Hull 1988, p.217).

One major flaw of the replicator-based theory of evolution, as correctly pointed out by Hull (1988), refers to the fact Dawkins establishes a distinction between what is putatively preserved (replicators) and the mere instruments of such hypothetically preservation (vehicles/organisms). In fact, the very idea of an element preserved for ever and ever does not make any sense from the point of view of molecular biology. Actually, there is nothing to literally preserve, but structures, networks and their dynamics (Tyson et al. 2008). Or, in the words of Hull: "neither genes nor organisms are literally 'preserved'. (…) All that is needed in either case is the preservation of structure" [emphasis added by the author himself] (Hull 1988, p. 413).

The same reasoning was expressed by the American physicist Richard Feynman, in his analysis of the permanence and impermanence of matter and the nature of the brain/mind interface: "(…) the thing I call my individuality is only a pattern or dance, 'that' is what it means when one discovers how long it takes for the atoms of the brain to be replaced by other atoms. The atoms come into my brain, dance a dance, and then go out ─ there are always new atoms, but always doing the same dance..." [emphasis added by the author himself] (Feynman 1988, p. 244).

So, the impermanence of everything but structures and their dynamics precludes any firm biological (or physical) basis for the hypothetically distinction between replicators and vehicles. But the confusion secondary to the distinction between permanent replicators and evanescent vehicles goes further in their downplaying of the role of organisms as interactors. Or in the words of Hull: "Vehicles are the sort of thing that agents ride around in. More than this, the agents are in control. They steer, and the vehicles follow dumbly. (…) the picture that Dawkins' terminology elicits is that of genes controlling helpless and hapless organisms" (Hull 1988, p. 413).

Such conceptual apparatus could not thrive without a deliberate effort to efface the materiality of organisms as such. Helpless and hapless vehicles could not be made compatible with different empirical evidence about the materiality of organisms. And the evidence of such materiality emerges from common sense, taxonomy, ethology, and last but not least, philosophy and literary criticism, such as in the contemporary studies about the so-called non-hermeneutic field (Gumbrecht 2003).

The 'extended phenotype' is the Dumpty of the 'selfish gene' Humpty. One concept could not survive without the other. One needs to blur the materiality of organisms in order to downplay the relevance of organisms as such, and nothing better for such purpose than to make organisms and behavioral traits such as mating behaviors or the building of nests (to cite just two examples) just the very same thing ─ different dimensions of something called 'the extended phenotype'.

But organisms are not the single victims of such attempt to blur different structures and patterns; ecology as such does no longer exist under such logic. Selfish genes first highjack their vehicles (organisms) and, later on, extend their reach to any dimension of the biological world, engulfing both organisms and the web of their interactions. Ecosystems become arenas for the games played by the 'replicators'. Biology becomes nothing but molecular biology, but worst than that, a kind of molecular biology without any firm biological basis but the genetics of 'beans in a bag'.

GENEALOGICAL AND ECOLOGICAL HIERARCHIES DO NOT NECESSARILY OVERLAP

"The ecological hierarchy is not genealogical and does not coincide with the genealogical taxonomic hierarchy (…) the evolutionary process can be understood only if genealogical and ecological hierarchies are distinguished. The genealogical hierarchy consists of genes, chromosomes,

organisms, demes, species, and monophyletic higher taxa. Eldredge's ecological hierarchy consists of proteins, organisms, populations, communities, and ecosystems. The reason that the evolutionary process appears so complex is that these two hierarchies do not map neatly onto each other. The most than can be said is that they intersect at the organismic level" (Hull 1988, p. 401).

As discussed at length by Eldredge (1995), organisms do basically two, non-overlapping, things. The gene-centered approach deals with one of those activities, reproduction. But the dynamic of the ecological web deals both with reproduction and matter/energy transfers between different organisms and between abiotic and biotic elements, such as the energy provided by the sun incorporated into successive trophic levels. Such trophic levels define the position that an organism occupies in a food chain. Predator-prey interactions have a dynamic of their own (May 2001), and such dynamics is of course influenced by and exert influence upon the survival fitness of each one of the species belonging to such food chains (in a recursive way). Notwithstanding, such interactions do not coincide with the dynamics of reproduction itself. The differences may be subtle, but anyway relevant. The very concept of ecological 'niche' would not exist without such double dynamics, comprising reproduction and matter/energy transfers. Or, in the words of Eldredge:

"(…) local population has a pronounced economic effect on the local environment ─ the local populations of other species, and the physical environment as well. The economic effect each such local populations has, the role it plays in the interlocking network of energy flow through the system, is what ecologists mean by the term 'niche'" (Eldredge 1995, p. 185).

Let's move both backwards and then forwards. First, to the beaver swimming in Dawkins' plate 7, mentioned before. Such gorgeous beaver is not swimming 'in ITS' extended phenotype. This environment it's not ITS environment, but a setting co-constructed by Mr. Beaver and a variety of biotic and abiotic factors. A beautiful example of the variety and complexity of such interactions is discussed by Lafferty *et al*. (2007) in their assessment of the food webs of a salt marsh ecosystem. Additional examples and in-depth analyses are provided by Jablonka & Lamb (2006) profiting from their concept of 'animal traditions', i.e. an appraisal of animal behaviors and interactions that incorporates both synchronic and diachronic dimensions.

Then, forward, to the necessary distinction between the two above-mentioned dynamics. Again, recurring to Eldredge:

"Local populations play definitive, and specifiable, economic roles in local ecosystems. The moment-to-moment economic interactions among organisms, whether with fellow members of their own species or with organisms from other species, has nothing directly to do with the reproductive concerns that sexually mature individuals have during the breeding season" (Eldredge 1995, p. 185).

Eldredge's book comprises an imaginary dialogue between the so-called naturalists and the so-called ultra-darwinists, seated at the high-table British colleges reserve to their intellectual elite. I would take here a less elitist position. Instead of concluding for the victory of one of the sides of the decades-long debate about the proper units of selection (Genes? Organisms? Species? Supra-organismic structures such as colonies and hives?), I prefer to put my scarce money on all of them or rather on dynamic hierarchies. Hierarchies are pivotal here, because without hierarchies the very idea of complexity and the uniqueness of biology die and biology becomes physics written large (or little, whatever the side one chooses). Once again, I return to Hull, who defined the complex dynamic of hierarchies two decades ago:

"(…) as long as the traditional organizational hierarchy is taken as fundamental, then selection will be found to wander erratically from level to level, and consequently, explanations in terms of selection will be highly variable and contingent" (Hull 1988, p. 401).

PROPER CONCEPTS INFORM PROPER ANALYSES AND RESEARCH PROGRAMS: PROSPECTS FOR A RENEWED EPIDEMIOLOGY OF INFECTIOUS DISEASES

As discussed above, there is no longer the need ─ prevailing at the time Haldane, Fisher and Wright formulated their original theories (i.e. 50-60 years ago) ─ to oversimplify the biological basis of evolutionary dynamics to permit the development of population genetics or epidemiology. Such disciplines have benefited from the exponential growth of knowledge

and tools in the field of mathematics, statistics and computational biology. Challenges prevailing in the 1950s and 1960s, such as the accurate and timely diagnosis of inborn syndromes heritable through mechanisms grossly resembling Mendelian genetics were successfully addressed and incorporated into standard medical textbooks. On the other hand, the full understanding of the genetic basis of cancer remains a major challenge for both basic and clinical sciences. Much probably the remaining gaps are secondary to the fact the dynamics of cancer cannot be explained by mechanisms which are operative at the sole level of genes, but rather by complex interactions at the genetic, epigenetic and organismic levels (Jablonka 2004).

New quantitative methods, such as stochastic context-free grammars have been used to assess the nature of the epigenetic components of human genome dynamics (Pedersen *et al*. 2006). So far such analyses seldom incorporate the dynamics of viruses and bacteria in context, i.e. integrated into different environments and hosts. However, recent analyses have assessed the interactions of microorganisms with the immune response within and between individuals (for instance, in the proper understanding of bottlenecks taking place in the transmission of pathogens such as HIV ─ Haaland *et al*. 2009 and Hepatitis C Virus ─ Luciani & Alizon 2009).

As advanced by Hull (1988) and fully discussed by Hull *et al.* (2001) and Cohen (2004), immunological processes have an evolutionary dynamics of its own. So, the current state of the art in the molecular epidemiology of infectious diseases has already incorporated the complex interplay of different evolutionary dynamics, within and between individuals. We are still short of a comprehensive understanding of such phenomena, but progressing under a fast pace.

Much has been done in terms of better understanding the interplay between the dynamic of the immune response and the evolutionary aspects of different pathogens (see, for instance, the classic book by Frank (2002), as well as recent publications such as Luciani & Alizon 2009).

Evolutionary dynamic has been also incorporated into standard models on the spread of infectious diseases at the population level, such as the analytic strategies summarized by Dieckmann *et al*. (2005). However, such analyses have been based on the classic paradigm of the evolutionary synthesis of the 1950s/1960s, as advanced by Fisher, Haldane, Dobzhansky among others, and informed by parameters operating at the genetic level or rather parameters exclusively ascribed to genes, which are, de facto, both genetic and epigenetic. Such parameters comprise mutation rates, relative differences in terms of fitness and costs imposed by natural of artificial selection on pathogens (e.g. microbial resistance secondary to the use of antibiotics ─ Byarugaba 2009). Once again, one could argue that such models may work well irrespectively of the underlying mechanisms being genetic, epigenetic or both. But, as discussed in the present text, empirical development should evolve side by side with conceptual developments. This may be a less traveled ─ notwithstanding, a fundamental ─ road. A 'long and winding road' to be fully explored by evolutionary biologists, ecologists, biomathematicians, biostatisticians, experts in computational biologists, and, last but not least, epidemiologists. What man knows, man sees!

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