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Discussion

2002 Neodarwinism and infectious diseases transmission: An e-debate

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1. First question

Could you very briefly summarize, in a few sentences, the Neodarwinian theory at nowadays?

1.1. Response from Yannis Michalakis

Evolutionary change may be adaptive or not. Adaptive change, by definition is due to natural selection. Correlation between traits, due to, for example, ontogeny, genetic linkage or linkage disequilibrium may constrain adaptive change. Selection may operate at different levels, not necessarily in the same direction. Evolutionary change may be neutral. Mutation is not directed.

1.2. Response from Emily Lyons

So much is encompassed by the modern synthesis (or Neodarwinian theory) that it is difficult to summarize in a few sentences, but here goes. It is, of course, universally accepted in the evolutionary biology community that phenotype is the result of the interaction between genotype and environment ($G \times E$ interaction), and that mutation and recombination provide variation, the raw material for natural selection. However, researchers certainly disagree regarding the relative importance of G and E. In particular, I think that technology (pcr, sequencing, etc. . . .) has led to increasingly reductionist, genetic explanations, thereby minimizing the importance of the natural history and of the organism and its environment. As far as the impact of the modern synthesis on the study of infectious disease is concerned, I think the message is clear that mutation and selection are important components of disease biology and treatment.

1.3. Response from Francisco Ayala

Three different, though related, issues have been the main subjects of evolutionary investigations: (1) the fact of evolution—that organisms are related by common descent with modification; (2) evolutionary history—the details of lineages when split from one another and of the changes that occurred in each lineage; (3) the mechanisms or processes by which evolutionary change occurs. The evolutionary origin of organisms is accepted by virtually every biologist, with a degree of certainty "beyond reasonable doubt", implied when biologists say that the evolution is a "fact". The second and third issues go much beyond the general affirmation that organisms evolve. The theory of evolution seeks to ascertain the evolutionary relationships between particular organisms and the events of evolutionary history, as well as to explain how and why evolution takes place. Recent advances in a variety of disciplines, notably paleontology and molecular biology, have made possible enormous strides in our understanding of evolutionary history. Think, for example, of how much we now know about hominid evolution or about phylogenetic relationships among microorganisms. There have also been many recent advances in our understanding of evolutionary processes. The sequences of the human and many other genomes have opened up many questions for investigation, and significantly contributed towards answering some old, as well as new questions. For example, think of the number of genes and their organization in organisms and of genetic regulation and gene expression. Advances in informatics and quantitative analysis are contributors to many issues. There are questions that have been debated for years, which have been all but settled, such as the neutralist–selectionist controversy. It would take a brave true believer to maintain that amino acid replacements are mostly, or even often, truly neutral. It is now becoming clear that nucleotide evolution is not neutral either. GC composition, tRNA abundance and other factors militate against the

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neutrality of nucleotide mutations. I could go on identifying important advances in our understanding of evolutionary processes. We have developed sophisticated methods to monitor the role of natural selection in specific cases; major strides have taken place towards understanding parasite–host relationships; the evolution and function of social organization have been much aided by the expansion of sociobiological knowledge; genetics, ecology and statistics have much furthered the investigation of epidemics; and so on. It is very satisfying to be an evolutionist at present. Advances are happening at almost vertiginous speed, and important new issues are continuously becoming open to scientific research.

2. Second question

Until now, the theory of evolution remained somewhat speculative for the reason that our knowledge of the structure and function of the genome, the main actor and witness of evolution, was rudimentary (my last editorial). This is changing with the advent of megatechnologies, such as automatic sequencing, DNA chips and bioinformatics. How the theory of evolution could help channel and direct this technological effort so that more knowledge is obtained with less effort? In other words, if you were the main coordinator of this international technological effort, what would you change?

2.1. Response from Francisco Ayala

Substituting a populational framework for typological thinking is a (the?) fundamental advance that Darwin and the Neodarwinian synthesis have contributed to the study of evolution and, indeed, of organisms in general. A population approach to genomics is absolutely necessary and must be implemented as soon and as widely as possible (from its inception and for a number of years, I was in the advisory council of NIHs Human Genome Project and persisted in seeking to convince the council of the populational perspective: "the" human genome is not a reality). The comparative approach of evolutionary biology is an eminently successful strategy for developing null hypotheses and designing experiments. Proper sampling of DNA polymorphisms in human populations at successively smaller levels of geographic inclusion will help to understand the history and patterns of dispersion of our species. Investigating large DNA segments will give us insights about how natural selection (as well as drift and other processes) has shaped the genetic make-up and geographic structuration of our species. As we seek to understand the genetic causes and correlates of humanness, we need to sequence the genomes of chimpanzees and other primates. Due to the considerable investment required for sequencing full genomes, and the "law" of diminishing returns, we must pursue this primate–genome project with effective sampling designs.

2.2. Response from Yannis Michalakis

Technological advances open black boxes and offer mechanistic explanations/descriptions of biological processes. At the same time, they unavoidably raise new questions, requiring a populational framework as Francisco has already pointed out. I just want to add that population geneticists, a branch of new-darwinists, have already made a massive shift towards the analysis of genomic data: traditionally, theoretical population geneticists were more concerned with conceptual models of evolution while at present a very large proportion of population geneticists elaborate new methods for analyzing genomic data. It is likely, and at least desirable, that as new technologies become more and more applicable to the non-model organisms, other branches of Population Biology will use genomic data to address evolutionary questions.

2.3. Response from Emily Lyons

As Yannis has pointed out, tremendous advances have already been made by population geneticists in the analysis of genomic sequence data. With the advent of these 'megatechnologies' we are afforded the possibility of examining the past (selection, recombination, mutation, linkage disequilibrium, etc. . . .) in a whole new way. This approach is extremely powerful but at present the technology is far more advanced than the tools we have for analysis. As the main coordinator of this technological effort, I would endeavor to get more mathematicians and statisticians interested in biological problems. Algorithms for gene finding, fine scale gene mapping, phylogeny construction, detection of polymorphism will undoubtedly enhance our ability to exploit the genomic resources available. Progress, in this post-genomic era, is to be made at the interface of mathematics, statistics, computer programming and biology thereby necessitating a truly collaborative effort between these disciplines.

Additionally, given that it is now possible to sequence whole genomes more and more quickly, I would suggest that more than one genotype of the same species (field isolate versus lab isolate) be sequenced as much can be gained from simple sequence comparisons, particularly when there are particular phenotypes associated with the genotype.

3. Side question from Michel Tibayrenc

Dear Francisco, since you were involved in the NIH board, do you know what happened with the "Human Diversity Genome Project" supported by Cavalli-Sforza, if I am not wrong?

3.1. Response from Francisco Ayala

No, at least, not with sufficient detail to comment about it.

There is another activity, along the lines of what I called the "Primate Genome Project" in my previous e-mail. This activity has been led by Morris Goodman (with me as a co-principal) and sponsored by the American Academy of Arts and Sciences and the NSF. We have had three meetings/symposia, about 1 year apart. The idea is to have NSF sponsoring a full research program on the subject. At our first meeting, the participants were all in favor of pursuing the project and some suggested names for the project, such as the "Human Genome Evolution Project". I prevailed in convincing the group that an NSF project with a separate budget-line item including the phrase "human evolution" would die, as soon as one of a number of US Congressmen happened to discover it. Something like "Human Variation", or "Primate Genome" is more likely to survive.

3.2. Comments from Michel Tibayrenc on the first responses

According to his answer to the first question, Francisco is a happy and optimistic evolutionist. However, many of the progresses he talks about are hopes rather than realities, since they are based on the in-depth knowledge of genome structure permitted by modern megatechnologies.

Responses to the second question: Francisco informed us about his valuable action in the NIH human genome committee, and underlines the need for a "Human Diversity Genome Project", a view which I definitely share (Tibayrenc, 2001).

Yannis speaks rather about a *downstream* use of genomic and postgenomic data by evolutionary biology, while Emily shares my concern (Tibayrenc, 2001) about the gap between technological and conceptual progress, and proposes to *upstream* direct the technological efforts by evolutionary concepts. In the framework of various pathogen sequencing projects, I have been advocating for years for the sequencing of at least two strains for each species, selected so that they are as phylogenetically distant as possible according to multilocus markers.

The three of you definitely agree on the invaluable future contribution of megatechnologies to the evolutionary science: data rather than speculation.

4. Third main question

It is now quite admitted that: (a) the host's genetic diversity plays a major role in the transmission and severity of infectious diseases (see the studies by Alain Dessein in Marseilles on man susceptibility to schistosomiasis); (b) most pathogens have a considerable genetic diversity and the diversity of their virulence genes and of their drug-resistance genes is epidemiologicaly highly relevant. However, specialists working on either hosts or pathogens poorly interact, and it is the very ecological niche of infection, genetics and evolution to try and integrate these lines of research, since there is here only one evolutionary phenomenon: the co-evolution host/pathogen. Unfortunately, this type of holistic research is hard to settle. Could you suggest an example of field research or experimental research based on this principle, and taking into account the host and the pathogen (and the vector in case of vector-born disease)?

4.1. Response from Francisco Ayala

Some parasites store in their genome sets of antigenic variants and they switch expression from variant to variant in order to escape recognition by the immune response of the host directed at previously expressed variants. The evolution of the sets of variants and of the switch mechanisms has been the subject of numerous investigations in a great variety of parasites. This evolution can only be understood by reference to the immune system of the host. One interesting question concerns the degree of diversity among the sets of antigenic variants. For example, the spirochete *Borrelia hermsii* (which causes Lyme disease and is transmitted by ticks) is controlled by IgM antibodies with relatively low affinity and high cross reactivity (Barbour and Bundoc, 2001). In contrast, many parasites are controlled by the more highly specific IgA and IgG antibodies. An interesting question is whether *Borrelia* has evolved greater molecular distance between variants than parasites controlled by the highly specific IgA antibodies. A recent paper (Rich et al., 2001) provides an affirmative answer. The *vsp* alleles (encoding surface lipoproteins) differ by 30–40% in amino acid composition, which is achieved by intragenic recombination. Many fascinating questions arise concerning the diverse evolution of antigenic variants and their switching mechanisms. These questions can be best, or only, understood by joint consideration of host and parasite evolution. One situation occurs in the highly diverse *var* genes of *Plasmodium falciparum*. Each parasite exports only one *var* type to the erythrocyte surface, but a clone of parasites switches among *var* types (Smith et al., 1995). On the contrary, *P. vivax* (which diverged tens of millions of years ago from *P. falciparum*) expresses in each erythrocyte several *vir* genes (out of the 600–1000 copies per haploid genome; del Portillo et al., 2001). Examples of the coevolution of host, parasites, and vectors can be found in Frank (in press).

4.2. Response from Yannis Michalakis

I can think of no example that explicitly takes into account both host and parasite genetic variabilities, where the genes directly involved in the interaction were fully characterized. There are examples, however, where enough was known to address evolutionary questions. The authors of such studies knew that they were dealing with a variety genotypes of hosts and parasites. The examples that pop up in my mind are: (i) the studies of Curt Lively's group on the interaction

between the snail *Potamopyrgus antipodarum*, intermediate host of a trematode parasite (*Microphallus* sp.); for instance, Lively and Dybdahl (2000) showed that sympatric parasites infected locally common host genotypes more often than locally rare genotypes, a mechanism at the basis of the Red Queen hypothesis; (ii) the studies of Dieter Ebert's group on the interactions between the crustacean *Daphnia magna* and its bacterial parasite *Pasteuria ramosa*; for example, Carius et al. (2001) showed that genetic variability for resistance/infectivity existed in host and parasite populations and that parasites were more successful in infecting hosts of the genotype in which they were originally isolated, while Little and Ebert (2001) examined the temporal pattern of variation of host resistance and parasite infectivity; (iii) the studies of Jeremy Burdon's group on the interaction between the plant *Linum marginale* and its rust *Melampsora lini*; for example, Burdon and Thrall (2000) consider the variability of resistance and virulence at multiple spatial scales and the consequences of such variability on the emerging patterns of disease. I obviously owe apologies to the many colleagues whose work should have popped up before the above stated examples.

4.3. Response from Emily Lyons

Michel, I disagree with you slightly. I think that at one time there was a lack of interaction between people working on hosts and parasites, but in the last 5–10 years, I think, most researchers (particularly in evolutionary biology) recognize the importance of understanding the interactions of host-species with their biological enemies. In my opinion, more confusion comes from the definition of co-evolution versus selection pressure by parasites. There are hundreds of studies of the interaction of parasites with their hosts that reveal the effects of parasite pressure on host life-history characters such as survival and reproduction (a quick Pubmed search usingkeyword = host–parasite interactions brought up 200) but very few (as Yannis suggests) actually demonstrate the co-evolution when it is distinguished from simple directional selection, coadaptation or sequential evolution. Often when you look for coevolution (cycles of parasite response to host characteristics and host response to parasite pressure) it is very difficult to find. There are a few examples and discussions of gene-for-gene coevolution (Thompson and Burdon, 1992; Flor, 1956).

As far as studies that try to integrate all of the components of a host–parasite–vector system and the consequences for population dynamics of all three (or at least the host and parasite) the Silene *latifolia*(alba)–*Microbotryum*(Ustilago) *violaceum*plant–pathogen system, work done by Antonovics et al. (1994) is particularly thorough. As Yannis has already mentioned Curt Lively's work, I just want to add the work of Mark Woolhouse and Joanne Webster on snails–schistosomes as another example of integrative work on host–parasite systems.

5. Last question

Based on your expertise as an evolutionist, which kind of practical recommendations would you make to public health decision makers for a better use of antibiotics in human and veterinary medicine?

5.1. Response from Francisco Ayala

Antibiotics should only be used whenever they are indispensable, in both human and veterinary medicine. Whenever antibiotics are used in humans, a cocktail of two, preferably three appropriate antibiotics would eliminate all bacteria, without allowing for the survival of a few resistant mutants. The probability of a resistant mutation to a particular antibiotic is likely to be about 10^{-9} or 10^{-10}. Therefore, such mutations are likely to arise in an individual suffering from an infection. If only one antibiotic is used, the resistant mutations will multiply and constitute a reservoir, which will make the particular antibiotic ineffective if the pathological infection reoccurs. The probability of a double resistant mutation is 10^{-18} to 10^{-20}, which makes it unlikely that it will arise in any one patient.

The same considerations apply to antibiotics used in veterinary medicine, when treating an individual animal, usually a pet. The considerations also apply to the treatment of cattle, chickens, and other animals (and their products, such as milk) bred in large numbers to provide food for humans. If the animals are numerous (as in chicken farms), the dangers of a double-resistant mutation are much greater. Thus, extreme caution is called for, lest resistant bacterial strains arise, and be passed on to humans.

5.2. Response from Yannis Michalakis

I agree with Francisco's comments. The only thing I could add, is a comment on the costs of antibiotic resistance. Indeed, it is often the case that antibiotic resistant bacteria incur a cost in the absence of an antibiotic treatment. This cost puts them at a disadvantage when in competition with antibiotic sensitive bacteria in antibiotic-free environments. The rationale behind Francisco's first sentence, that "antibiotics should only be used whenever they are indispensable" is partly based on this cost: antibiotic resistance will not evolve unless antibiotics are very frequently used, because antibiotic resistance is deleterious in the absence of antibiotics. Many experimental studies have shown, however, that unfortunately this cost is transitory: compensatory mutations restore the fitness of antibiotic resistant bacteria even in antibiotic-free environments. This provides another reason for using antibiotics only when they are indispensable: not only the spread of resistance would be impeded by such a policy, but the opportunity for compensatory mutations to arise would be decreased as well. The existence of such compensatory mutations could also provide another reason for the simultaneous use of "many" (i.e. >1) antibiotics: not

only the probability of appearance of multiply resistant bacteria is weaker, but also the compensation of their fitness costs will be much more difficult, at least if these costs interact in a non-additive way.

5.3. Response from Emily Lyons

I am not well versed in the latest antibiotic resistance literature, but certainly knowledge of truncation selection suggests that human and veterinary health providers should be cautioned to use antibiotics sparingly and in all cases, the courses should be taken to completion to minimize the occurrence of resistant mutants.

6. Concluding remarks from Michel Tibayrenc

It is urgent that clear and strict policies on the use of antibiotics are internationally edicted, and it is clear that evolutionists have much to contribute on this point. I thank you very much for your kind and very valuable contribution to this e-debate.

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Emily Lyons (USA) is a PhD student studying the population genetics and evolution of two human malaria species, *Plasmodium falciparum* and *Plasmodium vivax*. She studied both philosophy and biology as an undergraduate and is always keen for a debate. She has worked on plant–fungal and snail–trematode interactions and is deeply interested in the role of evolutionary biology in the solution of medically important problems. She is supported by a Wellcome Trust Prize Studentship at the University of Oxford.

Yannis Michalakis, born in Athens (Greece) is sometimes Greek and sometimes French (but rarely both). He is Directeur de Recherches at the Centre National de la Recherche Scientifique (CNRS). His research focuses on the evolutionary biology of host–parasite interactions, and more specifically on the coevolution of life-history traits, the evolution of virulence, local adaptation, parasite transmission strategies and the evolution of genetic systems. He is author of 49 papers and book chapters.

Francisco J. Ayala, born in Madrid (Spain) is American. He is the Donald Bren Professor of Biological Sciences and Professor of Philosophy at the University of California, Irvine. He has been a member of the President's Committee of Advisors on Science and Technology, and President and Chairman of the Board of the American Association for the Advancement of Science. His honors include election to the National Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society. He has received numerous prizes and honorary degrees. His research focuses on population and evolutionary genetics, including the genetic diversity of populations, the origin of malaria, the population structure of parasitic protozoa, and the molecular clock of evolution. He is author of 18 books and more than 700 papers. His areas of interest concern: evolutionary biology; including the teaching of evolution in the schools; genetics, including genetic engineering and the Human Genome Project; the interface, including perceived conflicts, between science and religion. The use of science and technological expertise in the court of law; the ethical and social dimensions of science.