Recombination rate and selection strength in HIV intra-patient evolution
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Rate of adaptation in large sexual populations
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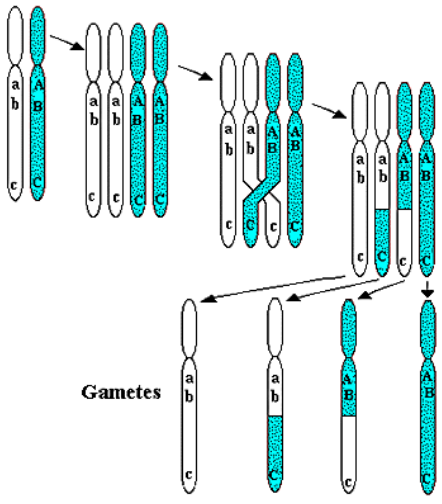
Population genetics has a long-standing and unique tradition among biological disciplines in featuring a strong and important role of modeling. Starting with the works of the founding fathers S.G. Wright, R.A. Fisher and J.B.S. Haldane, and continuing with the neutral theory of M. Kimura, quantitative analyses have played a much stronger role than in other fields of biology, as it is witnessed by the concise and most readable introduction to the subject provided by J. Gillespie (other reference books on the subject are Hartl and Clark, 2006; Lynch and Walsh, 1998 and the more mathematically inclined Ewens, 2004). More recently, data on genomic sequences and their continuously decreasing costs have finally permitted us to have a first-hand direct hold on the evolution processes at work within biological populations. The combination of these two elements has produced a spectacular surge in activity, which goes far beyond the genome-wide association studies that make the titles in the popular press for their relevance to human diseases.

A number of fundamental questions remain indeed wide open and could benefit from this unique state of things. Among them, genetic recombination, the role of sex and optimal levels of outbreeding in evolution exert a special fascination. Recombination refers to the process by which a molecule of DNA is broken and then joined to a different molecule. A notable example is the recombination between the paired chromosomes inherited from each of one's parents, occurring during meiosis in sexual reproduction. A scheme of the processes is shown in the figure below. The frequency of recombination between two locations depends on their



Crossing-over and recombination during meiosis

distance on the sequence. The increase of crossover rates for genes sufficiently distant on the same chromosome leads to a rapid decorrelation of their evolutionary history and, as a consequence, of the correlations in the alleles observed in a sampling of the population at a given time. Crossing-over shown above is one example of recombination but exchange of chromosomal chunks is not unique to meiosis: for example, clonally reproducing bacteria and viruses also feature important rates of recombination via various genetic mechanisms.

The major difference between point mutations at a single base and recombination is that the latter leads to major global reassortments of the genetic chromosomal material. Recombination can speed up evolution as it permits ``parallel occurrence'' of mutations, i.e. having two beneficial mutations occurring in different individual in the population and getting combined in a single individual via their sexual mating and recombination (Fisher, 1930 ; Muller, 1932). This should be contrasted to the case without any recombination where two mutations should occur in the very same individual, an event that takes much longer times. Recombination can also be a nuisance, though. Interactions among proteins and other cellular components make some pairwise (or multiple) combinations of alleles more fit than others. These interactions induce two-point (or higher-order) correlation effects that go under the name of epistasis. The nuisance of recombination is that ``good'' combinations of alleles can be broken up and fitness be decreased.

Whether or not recombination speeds up evolution and adaption is therefore an issue without a black or white answer and this produces endless discussions in the literature (Crow and Kimura, 1965; Maynard Smith, 1968; Felsenstein, 1974; Barton, 1995; Barton and Charlesworth, 1998). The presence of a sharp transition and maximum in the curve of fitness vs recombination rate was recently demonstrated in (Neher and Shraiman, 2009) for two simple epistatic models. The upshot is that a productive approach manifestly requires a quantitative knowledge of the evolutionary parameters. The difficulty in estimating recombination rates is that their effects are usually mixed up with selection, mutation rates, stochastic fluctuations and migration and the various contributions are hard to disentangle. Even assuming a purely neutral theory and the so-called coalescent model (see, e.g., Hein et al., 2005) the inference of recombination rates from a sample of the population poses a formidable Monte-Carlo computational challenge (Hudson, 1990).

The first recommended paper (Neher and Leitner, 2010) shows that HIV evolution within a single patient, despite its complexity, allows for effective estimations of the recombination rates. Diversity within the population can be generated both by possible co-infection of the same patient with different variants of the virus and/or divergence within the population (which applies even for patients initially infected by a single viral strain). Their genetic material will then be reshuffled by recombination and results in additional new variants that drift in the space of genomic configurations. The speed of this drift is crucial to escape the highly effective chasing by the immune system and, more recently, the effects of anti-drug treatments (see, e.g. Nora et al., 2007). Data on the viral population within the patient are available with a typical sampling frequency of a few months, providing for a unique opportunity to observe evolution in action. Neher and Leitner attack the problem by a combination of data analysis and modeling of the evolutionary dynamics in its impact upon the genetic composition of the population. By analyzing the temporal changes within the latter, they demonstrate that the rate of recombination can be effectively inferred. The work has several points of interest. On one hand, the same tools can be employed in other biological situations and the forthcoming higher time resolution data on HIV. Furthermore, recombination is a crucial element to take into account in the modeling of infection (see, e.g.,

Perelson and Nelson, 1999) and reliable estimates of its rate are highly precious. Finally, the work provides for a biologically relevant and fascinating motivation to the theoretical problem on the speed of adaptation, which was first considered in clonal populations (Gerrish and Lenski 1998; Desai and Fisher 2007). The extension to the case with recombination requires further non-trivial analytical tools and methods even in simple models of recombination and evolution (Cohen et al., 2005 ; Rouzine and Coffin, 2005 ; Neher et al., 2009). As illustrated in the conclusion of the second recommended paper (Neher et al., 2009), many important problems remain open, though, and they pose important challenges that are well-defined and quite appropriate to be taken up by theoretical physicists.

References

N.H. Barton, A general model for the evolution of recombination. Genet. Res. 65 123–145, (1995).

N.H. Barton & B. Charlesworth, Why sex and recombination? Science, 281, 1986–90, (1998).

E. Cohen et al. Recombination dramatically speeds up evolution of finite populations. Phys Rev Lett 94 098102, (2005).

J. Crow, J. & M. Kimura, Evolution in sexual and asexual populations. Am. Nat., 99, 439–450, (1965).

M.M. Desai & D.S. Fisher, Beneficial mutation selection balance and the effect of linkage on positive selection. Genetics, 176, 1759–1798, (2007).

W.J. Ewens Mathematical *Population Genetics : Theoretical Introduction* Springer, Berlin (2004).

J. Felsenstein, The evolutionary advantage of recombination. Genetics, 78, 737–756, (1974).

R.A. Fisher, *The Genetical Theory of Natural Selection.* Clarendon Press, Oxford, (1930).

P.J. Gerrish & R.E. Lenski, The fate of competing beneficial mutations in an asexual population. Genetica, 102, 127–144, (1998).

J. Gillespie *Population Genetics : A concise guide.* The Johns Hopkins University Press; 2nd edition (2004).

D.L. Hartl & A.G. Clark *Principles of Population Genetics.* Sinauer Associates, Inc.; 4th edition (2006).

J. Hein, M.H. Schierup & C. Wiuf *Gene Genealogies, Variation and Evolution – A Primer in Coalescent Theory*. Oxford Univ. Press (2005).

R.R. Hudson, Gene genealogies and the coalescent process. Oxford Surveys in Evolutionary Biology, 7, 1-44, (1990).

M. Lynch & B. Walsh, *Genetics and Analysis of Quantitative Traits.* Sinauer Associates; 1 edition (1998).

J. Maynard Smith, Evolution in sexual and asexual populations. Am. Nat., 102, 469–473, (1968).

H.J. Muller, Some genetic aspects of sex. Am. Nat., 66, 118–138, (1932).

R.A. Neher & B.I. Shraiman Competition between recombination and epistasis can cause a transition from allele to genotype selection. Proc. Nat. Acad. Sci. USA, 106(16), 6866-6871, (2009).

T. Nora et al Contribution of recombination to the evolution of human immunodeficiency viruses expressing resistance to antiretroviral treatment. J Virol 81, 7620-8, (2007).

A.S. Perelson & P.W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo. SIAM Review, 41, 3-44, (1999).

I.M. Rouzine & J.M. Coffin. Evolution of human immunodeficiency virus under selection and weak recombination. Genetics 170, 7-18, (2005).