



100 YEARS AGO

Symbol for Partial Differentiation. “The insufficiency of this notation is not forgotten, however, although its advantages over the different devices of Euler and Lagrange are recognised...”. I am glad to think that a pure mathematician sees the difficulty met with by users of mathematics. I wish that men who write to me privately would publish their remarks. One correspondent says: “I think ‘the mathematicians’ made a rather stupid blunder when they introduced ∂ for partial differentiation. This way: nearly all differential coefficients are partial; even a complete one (assumed complete) may become partial by extension of the field of operation. So an old investigation of Kelvin’s, for example, using d throughout, is, by ‘the mathematicians’, replaced by the same using ∂ throughout, except one or two here and there! What is the use? It gives a lot of trouble and as the printers haven’t always ∂ ’s, or proper sized ∂ ’s, it makes bad work. It should have been ∂ itself that was introduced for the exceptional use, thus making next to no alteration in the classical investigations.” These are indeed my own views, but as my pupils go forward to University examinations I advise them to adopt the fashion which is likely to please the examiners.

From *Nature* 17 July 1902.

50 YEARS AGO

Messrs. Blundell Rules, Ltd., Chaul End Lane, Luton, Beds, have issued a small handbook of 22 pages (price 6d.) describing their range of slide rules, and giving examples of the uses of the various patterns. Thus, in addition to the usual rules in various styles graduated for simple mathematical operations, there are others with log–log scales, commercial calculators, electricians’ scales with appropriate quantities, and a timber calculator. Most of these scales are made entirely of a white plastic material, based on vinyl chloride–vinylidene chloride copolymers, with a ‘satin’ finish. It is claimed to be resistant to water, most chemicals and fungi. It is strong, and the scales are sharp and clear; in some patterns the tension of the slide can be adjusted. Model A.G.1 (£1 13s.), a simple general-purpose rule, has the usual *A, B, C, D* scales, and also scales for reciprocals, cubes and mantissæ; additional red lines on the cursor provide for finding areas of circles of given diameter.

From *Nature* 19 July 1952.

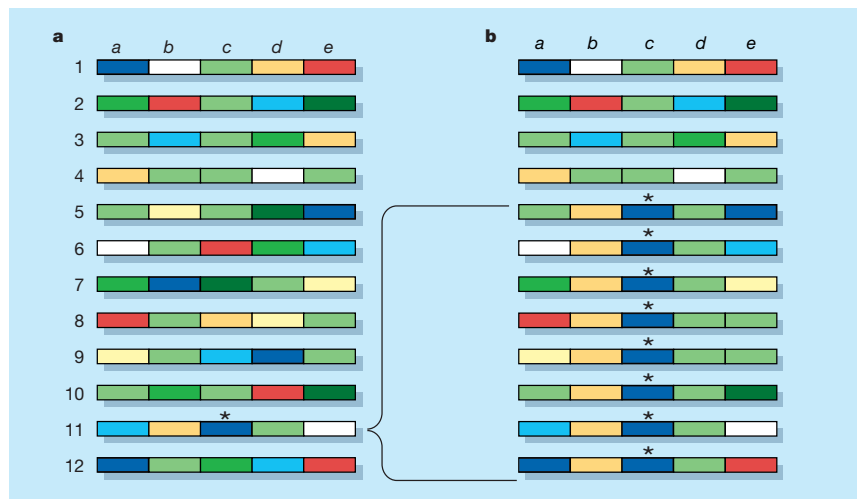


Figure 1 Genetic hitchhiking. a, A single chromosome with 5 genes (*a–e*), from 12 isolates, is shown. Each gene has considerable variation (it comes in different alleles, depicted by different colours). When a favourable mutation occurs (asterisk), it increases in frequency (b), taking not only the blue version of gene *c* to high frequency, but also the yellow form of gene *b* and the green form of gene *d*. These three genes end up losing most of their allelic variation after such ‘hitchhiking’. Genes farther away from the favoured gene *c* have undergone exchanges with other chromosomes (recombination), so the loss of variation decreases with greater distance from the selected gene.

evolution — there was no strong indication that natural selection had distorted the pattern of variation. They discovered 159 variable positions, including 11 silent changes, within these sequences. One weakness, not unique to this study, was in accepting the public databases as error-free, so any sequencing mistakes would have been incorporated into their model as variation. But even if error rates were at the high end of credibility, the level of variation in these data still exceeds that of the other studies^{4,5}.

This sets the stage for the approach of Mu *et al.*², who re-sequenced portions of 204 genes in the largest survey so far of variation on chromosome 3 of *P. falciparum*. The authors obtained more than 218,000 base pairs of coding and non-coding sequence from 5 widely divergent isolates, and found 238 single changes (62 of which were silent and 31 of which were in non-coding sequence) and 165 microsatellite variants. From these data Mu *et al.* estimate a relatively high level of variation at silent sites, consistent with a time of common ancestry of 150,000 years ago.

All these details are important because there have been several competing explanations for the many different estimates of *P. falciparum* ancestry. One proposed explanation is that *P. falciparum* is a recently evolved species, with mutation rates that vary wildly along its chromosomes, giving different pictures depending on the genes studied. Another is that *P. falciparum* is ancient but in the recent past suffered a massive restriction (‘bottleneck’) in the number of surviving lineages and consequently lost most variation — leading to the relatively young date of common ancestry calculated in studies that,

by chance, failed to sample any divergent but rare alleles. A third is that natural selection favoured novel mutations, such as those for drug resistance, and that as these mutations increased in frequency, they dragged linked genes (in a process known as ‘hitchhiking’; Fig. 1) with them. This too would create an impression of little variation in some genes. Although it might not settle the question, Mu and colleagues’ study² of DNA sequence variation is far larger than its predecessors, and provides strong evidence that *P. falciparum* is diverse enough to raise a greater challenge for public-health measures.

In a separate analysis³ the same group provide a beautiful example of genetic hitchhiking. Wootton *et al.*³ were looking at variation in the ability of *P. falciparum* to resist the widely used antimalarial drug chloroquine. They studied microsatellites in 87 worldwide isolates of the parasite, and found that a narrow region of chromosome 7 — including the *pfert* chloroquine-resistance gene and flanking sequences — shows little variability among chloroquine-resistant isolates but is more diverse among sensitive isolates. Further analysis supported the idea that there are at least four independent forms of *pfert*, which are rapidly becoming more common in different parts of the world. The inference that selective pressures (in this case, the use of chloroquine) cause such localized increases in gene frequency is receiving attention elsewhere⁸, but a technical advantage of *Plasmodium* is that it has just one copy, not two, of each chromosome. The results show that complex combinations of mutations arise readily. So, in principle, *P. falciparum* might rapidly develop resistance to multiple drugs. The genes also