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The curious case of a hapless mathematical contribution to biology

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1 **The curious case of a hapless mathematical**
2 **contribution to biology**

3 **Chromosome inversions in *Drosophila*, 1937-1941**

4 **Eric Tannier**

5 **Abstract** This is the story, told in the light of a new analysis of historical
6 data, of a mathematical biology problem that was explored in the 1930s in
7 Thomas Morgan's laboratory at the California Institute of Technology. It is one
8 of the early developments of evolutionary genetics and quantitative phylogeny,
9 and deals with the identification and counting of chromosomal rearrangements
10 in *Drosophila* species from comparisons of genetic maps. A re-analysis of the
11 data produced in the 1930s using current mathematics and computational
12 technologies reveals how a team of biologists, with the help of a renowned
13 mathematician and against their first intuition, came to an erroneous conclusion
14 regarding the presence of phylogenetic signals in gene arrangements. This
15 example illustrates two different aspects of a same piece: 1) the appearance of
16 a mathematical in biology problem solved with the development of a combi-
17 natorial algorithm, which was unusual at the time, and 2) the role of errors in
18 scientific activity. Also underlying is the possible influence of computational
19 complexity in understanding the directions of research in biology.
20

21 **Keywords** history of biology · evolutionary genetics · chromosomal inversion ·
22 genetic maps · statistics · computational complexity · scientific errors · history
23 of interdisciplinary studies · *Drosophila*

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24 *This is the first time in my life I believe in constructing phylogenies, and I have to eat*
 25 *some of my previous words in this connection. But the thing is so interesting that both*
 26 *Sttt [Sturtevant] and myself are in a state of continuous excitement equal to which we did*
 27 *not experience for a long time.*

28 Theodosius Dobzhansky, letter to Milislav Demerec 1936

29 *I am rather surprised to find myself figuring out hypothetical phylogenies for the*
 30 *Drosophila species, and taking them more or less seriously — after all the*
 31 *uncomplimentary remarks I've published about such procedures.*

32 Alfred Sturtevant, letter to Otto Mohr 1939

33 These two quotes attest to the renewed interest in phylogeny during the
 34 first half of the twentieth century. Marks of enthusiasm such as these, associ-
 35 ated with the revival of this old discipline, were common. Among other possible
 36 reasons, they are due, on the one hand, to the use of cytological and genetic
 37 comparisons, offering direct access to hereditary material, and on the other,
 38 to the use of quantified methods, often associated with objectivity. According
 39 to Anderson (1937), cytology was like “looking at the cellar window”, and is
 40 “evidence as to the germplasm itself and is, therefore, of more fundamental
 41 importance than the mere architecture erected by the germplasm itself.” For
 42 Turrill (1938), chromosomes provided “high-powered morphology”. For Mc-
 43 Clung (1908), “The chromosomes are the determinants of characters”, and
 44 “one cell is sufficient for the identification of the species”. “Were our knowl-
 45 edge of cell structure in the grasshopper complete enough we might erect a
 46 system of classification based upon cytological characters, just as reasonably
 47 as we have designated one using external anatomical structures” (McClung,
 48 1908). As for quantification, the comparisons allowed by precipitin reactions
 49 (Strasser, 2010b) made Boyden (1934) write that “The fact that naturalists
 50 of recent times have so often forsaken the study of phylogeny is due more to
 51 the feeling that such a study is likely to yield little certain progress than to
 52 the belief that the problems of phylogeny are unimportant or sufficiently well
 53 analyzed.”

54 Of course, the use of both “semantic”¹ characters and quantification, driven
 55 by the development of sequencing techniques and computers, was only fully
 56 realized in the 1960s by the founders of Molecular Evolution (Suárez-Díaz,
 57 2009; Dietrich, 2016). However the evolutionary genetics program that began
 58 in Thomas Morgan’s laboratory in 1914, and was subsequently continued by
 59 the partners turned rivals Alfred Sturtevant and Theodosius Dobzhansky, had
 60 similar epistemological characteristics².

61 The aim of this article is to give an account of a particular moment of this
 62 research, focusing on Sturtevant’s attempts, over several years and with sev-
 63 eral successive Ph.D. students, to quantify the number of inversions between
 64 homologous genetic linkage groups in two *Drosophila* species. Some aspects

¹ According to the vocabulary of Zuckerkandl and Pauling (1965), this is the directly transmitted hereditary material, and not one of its products, see also Dietrich (1998).

² Despite crucial differences in the biological objects have also been discussed (Darden, 2005).

65 of this research, in particular the attempts to quantify evolutionary diver-
66 gence, the involvement of the mathematician Morgan Ward, and the errors
67 that resulted, have been overlooked in historical accounts of the study of chro-
68 mosome evolution (Hagen, 1982, 1984; Kohler, 1994; Gannett and Greisemer,
69 2004; Smocovitis, 2006) and of the use of quantification in biology (Hagen,
70 2003; Suárez-Díaz and Anaya-Muñoz, 2008; Suárez-Díaz, 2010; Hagen, 2010).

71 In the 1930s the use of mathematics, and collaborations with mathemati-
72 cians was commonplace in biology, and particularly in evolutionary biology.
73 It was even central part to the construction of the modern synthesis (Bowler,
74 2003). However the type of mathematics in this example is unusual in that
75 it differs from that available to evolutionists, as developed for instance by
76 Fisher, Wright or Haldane for statistics and population genetics. Retrospec-
77 tively combinatorial and computational aspects are visible, which were handled
78 at the time with underlying³ systematically applied algorithms on permuta-
79 tions. Some of the questions addressed at the time were only solved 50 years
80 later, and some even remain unsolved today. The difficulties that mathemati-
81 cians encounter today with these problems were already visible in Sturtevant's
82 attempts. Nevertheless, after trying to solve the same questions myself with
83 today's mathematics and technology, I found three computational and nu-
84 merical approximations, initially acknowledged as such by the authors, which,
85 after consulting Ward, strangely turned into errors and led to a wrong bio-
86 logical interpretation. This curious case of an unfortunate use of mathematics
87 to solve an evolutionary question illustrates the presence and importance of
88 errors in the practice of science. We could also see it as an example of the of-
89 ten overlooked impact of computational intractability (Papadimitriou, 1993)
90 on biological research.

91 In the first part of this article, I provide some contextual elements con-
92 cerning the use of chromosomes in evolutionary studies, both worldwide and
93 in Thomas Morgan's laboratory, in order to highlight the originality of Sturte-
94 vant's research. In the second part I describe how Sturtevant progressed from
95 making the first genetic map to the challenge of counting inversions. Along-
96 side historical descriptions, I give my solutions to the described problems using
97 current scientific knowledge. In the third part, I discuss what this exercise can
98 teach us about the unexpected presence of combinatorial algorithmic consid-
99 erations in 1930s biology, and about the influence of errors and complexity in
100 both past and present research programs.

101 1 Chromosomes as documents of evolutionary history

102 In the first half of the twentieth century, the development of genetics and cytol-
103 ogy led several researchers and research teams to compare chromosomes and/or
104 linkage groups in order to establish evolutionary relationships and reconstruct
105 evolutionary histories (Hagen, 1982). New markers emerged to delimit and

³ *I.e* not explicit

106 classify species or construct phylogenies, such as: the number, shape and size
107 of chromosomes, their behavior during the cell cycle, the position of the cen-
108 tromere or the arrangement of genes. To cite only a few landmarks of this
109 development: at the International Zoological Congress in Boston in 1907, the
110 cytologist Clarence Erwin McClung stated that a character measured within
111 the cell, such as the number of chromosomes, could be considered as informa-
112 tive for phylogenetic classification as any morphological character (McClung,
113 1908). In 1915 in Berkeley, California, the plant geneticist Ernest Brown Bab-
114 cock gathered a team to work on the evolution of the flowering plant *Crepis*
115 and contributed to the foundation of the “Bay Area Biosystematists” (Ha-
116 gen, 1984; Smocovitis, 2009), an influential multidisciplinary group working
117 on plant systematics. In 1926, the International Congress of Plant Science
118 held a joint session involving taxonomists, cytologists and geneticists (Hagen,
119 1984). In 1937, the field was sufficiently established for Edgar Anderson, from
120 the Missouri Botanical Garden, to write an extensive review on the contribu-
121 tion of cytology to taxonomy in botany (Anderson, 1937). In 1938, Babcock
122 and his collaborator George Ledyard Stebbins Jr, who would become a leading
123 evolutionary biologist (Smocovitis, 2006), published the influential book *The*
124 *American Species of Crepis*, in which all the genetic and cytological knowledge
125 available at the time was harnessed to decipher the complex evolutionary re-
126 lationships between members of the the *Crepis* genus (Babcock and Stebbins,
127 1938; Smocovitis, 2009).

128 A comparable research program on the fruit fly *Drosophila*, the traditional
129 model organism from which genetics was first developed (Kohler, 1994), was
130 carried out in Thomas Hunt Morgan’s genetics laboratory, first at Columbia
131 from 1914 to 1928 and then at Caltech. It was initiated by Charles Metz, born
132 in 1889, who joined in 1912 Morgan’s laboratory at Columbia where he became
133 interested in cytology. Metz soon realized that his observation of *Drosophila*
134 chromosomes in anaphase possibly carried phylogenetic information because
135 different species had different chromosomal conformations. Combining data
136 for the presence or absence of microchromosomes and the state of two auto-
137 somes (fissioned vs. fused) in 12 *Drosophila* species, Metz managed to classify
138 chromosome organizations into five types. These types were then organized
139 into a tree, where the branches could be interpreted as evolutionary events
140 (Figure 1).

141 In article published in 1914, from which Figure 1 is reproduced, Metz
142 speculated that differences in chromosome types “may indicate an evolution
143 of chromosomes in the genus” (Metz, 1914). However, in his subsequent ar-
144 ticles on the description of chromosome types, Metz became more and more
145 cautious regarding any possible evolutionary interpretation (Kohler, 1994),
146 mainly because of the difficulty in assessing the homology⁴ between chromo-
147 somes via the technique of independent observation in different species. As

⁴ The term homology, in the sense of “common evolutionary origin”, was not commonly used at the beginning of the 20th century. The terminology was discussed and ranged from “allelomorph” to “corresponding”. I use the current terminology for the sake of consistency and clarity.

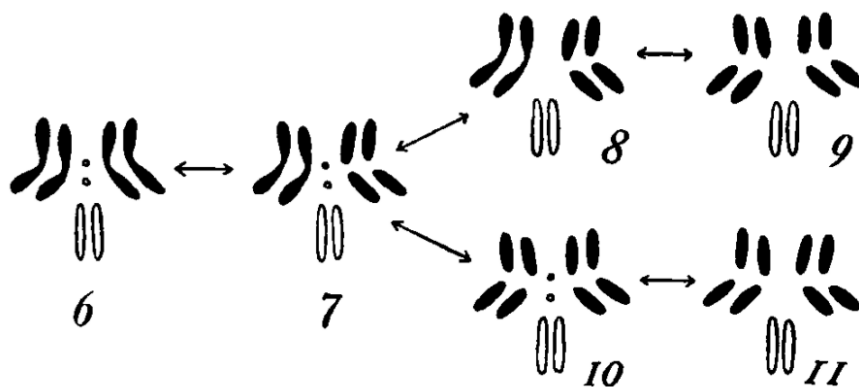


Fig. 1 Reproduction of Figure 1 from Metz (1914). The five different karyotypes from 12 *Drosophila* species, are organized into a tree with a wishful evolutionary interpretation. Nodes 9 and 11 represent the same type of chromosome organization, meaning that the two phylogenetic positions are equally possible. Reproduced with the kind permission of Wiley and the *Journal of Experimental Zoology, Part A: Ecological Genetics and Physiology*.

148 a result, his subsequent publications (Metz, 1916, 1918) seem more like an
149 organized catalog of chromosome types, with less evolutionary implications.

150 Then began the search for a technique to assess homology. One method
151 was to produce interspecific hybrids and observe coupled chromosomes during
152 segregation, but this showed little success with *Drosophila* species (Kohler,
153 1994). Hybrids could be produced but were almost always sterile. Two sub-
154 sequent techniques would prove more successful for assessing homology and
155 were explored in Morgan's laboratory: gene mapping on chromosomes (from
156 1917) and hybridization of polytene chromosomes (from 1936).

157 Charles Metz himself left Columbia University for Washington in 1914 and
158 did not participate further in the activities at Columbia, even though he be-
159 came an eminent *Drosophila* geneticist. However, while at Columbia he did not
160 work alone and his research program was continued by others. As mentioned
161 in the acknowledgments in his 1914 article (Metz, 1914), he benefited from the
162 help of a young student from Columbia, Alfred Sturtevant.

163 **2 Alfred Sturtevant and Comparative Genetic Mapping, 1921 to** 164 **1941**

165 2.1 Genetic maps and predicting inversions

166 Sturtevant, born in 1891, completed his doctorate in 1914 with Thomas Mor-
167 gan at Columbia University. One of his legendary achievements was to respond
168 to Morgan's remark, according to which the strength of the genetic linkage be-
169 tween genes, measured from the observation of phenotypic characters, could
170 be related to the physical distance between the genes on a chromosome. From

171 this idea, Sturtevant defined genetic distance as the percentage of crossing-
172 over between two genes, which he observed from the frequency of associated
173 phenotypes in *Drosophila ampelophila*⁵. As this distance was close to a linear
174 function, it was possible to position genes on a line. This led to the first genetic
175 map, which placed six genes on the “sex-linked” linkage group⁶ (Gannett and
176 Greisemer, 2004).

177 Following Sturtevant’s, the same research group produced several other
178 genetic maps. In particular, Morgan and Bridges’ 36-marker map of the X-
179 chromosome of *Drosophila melanogaster* (Morgan and Bridges, 1916) was dis-
180 puted by William Castle (Castle, 1918, 1919) and, by association, several other
181 researchers, who questioned the relevance of the linear model for depicting
182 chromosomes, with responses by Sturtevant et al. (1919); Morgan et al. (1920).
183 Even though each protagonist gave the impression of standing firm on his re-
184 spective position, the controversy helped clarify much of the theory, as well as
185 its underlying and *ad hoc* hypotheses.

186 The real starting point for evolutionary genetic studies was the discovery
187 of mutations in that linear structure. Inversions, *i.e.* evolutionary events re-
188 versing the orientation of chromosome segments, were hypothesized by Sturte-
189 vant (1921) based on the observation of differences in the arrangement of five
190 “corresponding”⁷ genes on chromosome 3 between *Drosophila simulans* and
191 *Drosophila melanogaster*. The inversion hypothesis was confirmed by adding
192 genes, while the comparative mapping carried out by Sturtevant and Plunkett
193 (1926), illustrated in Figure 2, presents a striking visual argument in support
194 of it⁸.

195 Inversions themselves had the same status as linkage groups, that is, they
196 were theoretical objects independent of any direct cytological observation. A
197 cytological demonstration of their existence would be made later with the
198 techniques of Painter (1933).

199 From this possibility of detecting mutations by comparing genetic maps,
200 Sturtevant developed a comprehensive research project in continuity with his
201 work with Metz. The aim was to map the genes of different *Drosophila* species,
202 assess the homology between these genes and, from the chromosome structure,
203 reconstruct the evolution of these species (Kohler, 1994). This research project
204 was not fully realized, although several publications and many unpublished

⁵ Renamed *melanogaster* shortly after.

⁶ Later named the X-chromosome in order to emphasize its peculiarity. The link between chromosomes and linkage groups was already well established, as can be seen by the natural use of “chromosome” in genetic studies from the 1910s onward.

⁷ *I.e.* homologous, see footnote 3. Homology was deduced from the similarity of phenotype variations during crossing experiments.

⁸ Several types of translocations, *i.e.* other mutations of the linear organization of genes along chromosomes, were predicted at the same time (Bridges, 1917; Mohr, 1919; Morgan et al., 1925) and later demonstrated using cytology (Muller, 1929; Dobzhansky, 1930). They were generally considered to be “deficiencies”, or abnormalities of karyotypes, possibly resulting from mutagenic conditions. By contrast, inversions were immediately seen as evolutionary patterns susceptible to being used in differentiating species, and thus be a character for taxonomy. Translocations were later used in plant taxonomy by Babcock and Stebbins (1938).

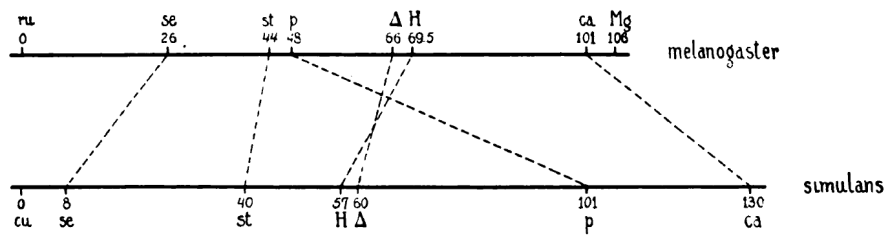


Fig. 2 Reproduction of Figure 1 from Sturtevant and Plunkett (1926): a graphic representation of gene arrangements supporting the existence of inversions and their utility for taxonomy. Linkage group 3 is compared in *Drosophila simulans* (below) and *Drosophila melanogaster* (above). Genes (points) are placed on the line (representing the chromosome or linkage group). Homologous genes are represented by dashed lines. Reproduced with the kind permission of *The Biological Bulletin*.

205 results⁹ confirm they made decisive advances as well as reveal some challenges.
 206 A close look at the mathematical techniques they use helps us understand the
 207 progressive introduction of quantification, and how, if it gives the impression
 208 of objectivity and fights a “methodological anxiety” (Suárez-Díaz and Anaya-
 209 Muñoz, 2008), it is not necessarily a guarantee of greater veracity or accuracy.

210 2.2 The first mathematical problem: the observed inversion distance

211 One of the challenges of studying chromosomal arrangements involves the de-
 212 tection of several successive overlapping inversions. Comparing two arrange-
 213 ments that differ by one inversion was easy. However if several overlapping
 214 inversions have occurred, which is likely if more distant species were com-
 215 pared, an additional difficulty arose. In 1937, Sturtevant, published with C.
 216 C. Tan, a Ph.D. student supervised by himself and Dobzhansky, a compari-
 217 son of the arrangements of 38 genes along all the chromosomes of *Drosophila*
 218 *melanogaster* and *Drosophila pseudoobscura* (Sturtevant and Tan, 1937). The
 219 comparative maps, inferred from the homology of genes deduced from similar
 220 phenotypic effects, are reproduced in Figure 3. Inversions are not as visible as
 221 in Figure 2 because the species are more distant and thus the accumulation of
 222 inversions has blurred the signal.

It is useful to carefully examine both the data and the discussion shown in Figure 3 from the 1937 article by Sturtevant and Tan. A first mathematical problem is stated: given a permutation of letters (the gene order in *melanogaster*), find a sequence of successive inversions transforming it into the alphabetical order (the gene order in *pseudoobscura*). This sequence should have the smallest possible number of inversions, as implied by the term “necessary” in the text. This is the parsimony argument, which was also proposed for comparing DNA or protein sequences by Camin and Sokal (1965). This minimum number has been subsequently named the *inversion distance* of a

⁹ Examined by Kohler (1994), who writes that the unpublished part is of wider significance.

legitimate. If the *pseudoobscura* sequence in each arm is arbitrarily taken as an alphabetical one (A B C . . .), then the *melanogaster* sequences become:

X L H F E B A D C K I J G M (7)
 II L D E F A C B (2)
 II R A C E B F D (4)
 III L C F E B A D (3)
 III R A E B C F D G (3)

The numbers in parentheses represent the numbers of successive inversions necessary to turn these sequences into alphabetical ones (in the case of X we are not yet certain that six inversions may not be sufficient). The mathematical properties of series of letters subjected to the operation of successive inversions do not appear to have been worked out, so that we are so far unable to present a detailed analysis. It does appear, however, that the five arms (taken together) are definitely more alike in the two species than could result from chance alone.

Fig. 3 Excerpt from Sturtevant and Tan (1937). Chromosome names are given in the column on the left; gene names range from A to M. Numbers in parentheses are the minimum number of inversions that are necessary to transform the arrangement of letters on a line (*melanogaster* arrangement) into the alphabetical order (*pseudoobscura* arrangement). In the paragraph below the letter arrangements, a working program for mathematicians and (not yet existing) computer scientists. Reproduced with permission from *Springer*.

permutation (Fertin et al., 2009). For example, the sequence on chromosome IIL can be transformed into the alphabetical order by two inversions as follows:

$$\underline{DEFACB} \rightarrow \underline{AFEDCB} \rightarrow ABCDEF.$$

223 The first inversion concerns the underlined segment *DEFA*, and the second
 224 inversion the segment *FEDCB*. It is easy, by enumerating all possible inver-
 225 sions, to see that for this example, one inversion alone cannot transform the
 226 initial permutation into the alphabetical order. So the minimum number, *i.e.*
 227 the inversion distance of permutation *DEFACB*, is 2. Computing this number
 228 becomes tricky when genes and inversions are more numerous.

229 2.3 Resolution with modern mathematics

230 Note that in the paragraph in Figure 3, Sturtevant and Tan recognized that
 231 for the X-chromosome their best scenario had seven inversions, but they were
 232 not certain six was impossible. No detail is given regarding their method for
 233 finding the scenario with seven inversions or the reasons why they doubted
 234 that seven was minimum number. They probably enumerated many scenarios
 235 and could not find one with less than seven, but enumerating all scenarios was
 236 considered too long or tedious a task. The cautiousness of their statement was
 237 retrospectively a good intuition, since

$$\begin{aligned}
& \underline{LHFEBADCKIJGM} \\
& \rightarrow \underline{ABEFHLDCKIJGM} \\
& \rightarrow \underline{ABCDLHFEKIJGM} \\
& \rightarrow \underline{ABCDEFHLKIJGM} \\
& \rightarrow \underline{ABCDEFHGJIKLM} \\
& \rightarrow \underline{ABCDEFHJIKLM} \\
& \rightarrow \underline{ABCDEFGHIJKLM}
\end{aligned}$$

238 is one of several possible *bona fide* sequences of six successive inversions. It
239 is possible to prove that six inversions are necessary, *i.e.* five is not possible,
240 using the lower bound found by Kececioglu and Sankoff (1995). They define
241 *breakpoints* as pairs of letters that occupy two consecutive places in the initial
242 arrangement, but are not consecutive in the alphabetical order. Thus a pair of
243 breakpoints comprises four letters. If, among those four letters, there are two
244 pairs of consecutive letters in the alphabetical order, the pair of breakpoints
245 is called an *edge*. With b the number of breakpoints, and m the maximum
246 number of edges that do not share breakpoints, Kececioglu and Sankoff (1995)
247 prove that the inversion distance is at least $\frac{2b-m}{3}$. In our case, $b = 9$ and
248 $m = 2$, which makes the lower bound strictly greater than 5.

249 The “detailed analysis” called for by Sturtevant and Tan (see Figure 3)
250 would have to wait several decades before it became possible with the help of
251 new mathematical and computational techniques (Fertin et al., 2009). However
252 even today, no closed formula or “good” algorithm, *i.e.*, an algorithm that
253 would not require the enumeration of the combinatorial structure, are known
254 to solve the inversion distance problem for any arrangement. Here I did not use
255 any canonical method to find the scenario with six inversions, such a method
256 does not exist. I found this solution while trying to prove that the 6-inversion
257 scenario did not exist, in order to confirm the statement of Sturtevant and
258 Tan (1937). To do so, I assumed its existence, derived some of the properties
259 it should have with the goal of arriving at a contradiction; instead this scenario
260 arose.

261 The fact that Sturtevant and Tan stated that the result was uncertain is
262 not anecdotal, it is actually important because later on their result was turned
263 into an error. While their passing statement was forgotten, the number seven
264 was taken at face value. Together with two other subsequent approximations
265 this would lead to an erroneous biological conclusion.

266 2.4 The second mathematical problem: the expected inversion distance

267 This brings us to the second mathematical problem stated by Sturtevant and
268 Tan, of a statistical nature. The last sentence in Figure 3 states that the
269 arrangements of genes in *pseudoobscura* and *melanogaster* “are definitely more
270 alike in the two species than could result from chance alone.” The statistical
271 problem then asks whether the observed gene arrangement has a significantly

272 lower inversion distance than a random arrangement. The answer requires the
273 computation of an expectation and a variance of the inversion distance for
274 a random permutation. An observation that cannot be attributed to chance
275 (if the observed value falls outside the standard error interval around the
276 expectation) can be considered as the sign of the common origin of the two
277 arrangements.

278 The word “definitely” in this sentence is interesting for our purpose be-
279 cause it illustrates the progressive extension of the quantification. It means
280 that intuitively, the inversion distances found between *melanogaster* and *pseu-*
281 *doobscura* do not appear to be attributable to chance. This intuition was then
282 turned into a statistical hypothesis in the follow-up paper by Sturtevant and
283 another student, Edward Novitski (Sturtevant and Novitski, 1941). Novitski,
284 like Tan before him, was first a student of Dobzhansky and continued with
285 Sturtevant after Dobzhansky’s and Sturtevant’s dispute (Novitski, 2005). In
286 each lab, he worked on chromosomes and evolution using different approaches.
287 While working with Sturtevant, he generated a large catalog of homologies,
288 some from the literature and some newly obtained via classical genetic tech-
289 niques, and carried out a more in-depth mathematical analysis of the 1937
290 data.

291 2.5 The call for a professional mathematician

292 After going over the statements of Sturtevant and Tan (those reproduced in
293 Figure 3), Sturtevant and Novitski announced that they had solicited the help
294 of Morgan Ward, a renowned mathematician from Caltech. Sturtevant himself
295 had a reasonable understanding of mathematics, and Novitski (2005) retro-
296 spectively praised his “mathematical mind”, compared with Dobzhansky’s.
297 However Sturtevant and Novitski probably felt that no easy technique could
298 solve this question and logically solicited the help of an expert.

299 Morgan Ward (1901-1963) entered Caltech in 1924 as a student, and be-
300 came a research fellow in 1928. Appreciated by many for his qualities as a
301 teacher, he apparently showed no particular interest in biology, though an ac-
302 knowledgement can also be found in an article by Dobzhansky and Wright
303 (1941), the only other biology paper, alongside the one studied here, featuring
304 his name. He was more interested in the contribution of his field to physics.
305 His expertise in number theory and Diophantine equations (Lehmer, 1993),
306 which involved the design of calculation methods on integer numbers, might
307 have convinced Sturtevant and Novitski to request his help. The exact mode
308 of collaboration is not known: it is just mentioned in the middle of the article
309 that Ward provided some help. We can suppose one or a few work sessions,
310 where the two mathematical problems, that of the inversion distance and its
311 statistical significance, were exposed and ways to compute the solutions were
312 discussed.

313 The solution they found to test whether the difference in arrangement
314 was indeed “more alike [...] than could result from chance alone”, was for

315 permutations of 6 genes or less, to enumerate all permutations and for each
316 one, to compute the inversion distance. Then they calculated the mean and
317 standard deviation of all inversion distances. For permutations of eight and
318 nine genes, 60 and 40 permutations were sampled at random instead of the
319 complete enumeration. For higher numbers, permutations were not sampled
320 and the expected inversion distance was obtained by a linear interpolation
321 from smaller number. Indeed, as admitted in the article, “For numbers of loci
322 above nine the determination of [the inversion distance] proved too laborious,
323 and too uncertain, to be carried out” (Sturtevant and Novitski, 1941).

324 They obtained a mean of 7.6 inversions for 13 genes (see Figure 4), leading
325 them to conclude that, in contrast to their initial intuition, “Evidently the two
326 species are not more alike than could easily result from chance alone”. The
327 use of the terms “definitely” in the sentence from 1937 quoted above and “ev-
328 idently” here suggests several remarks. First, the later statement states that
329 the earlier was evidently a wrong intuition, which tells us something about
330 the scientific personality of Sturtevant: he did not hesitate to admit to himself
331 his supposed error in strong terms. Second, if the latter statement corrects
332 the former by a quantitative assessment of the initial idea, we can note that
333 the intuitive aspect has not been fully eliminated. The authors, after having
334 considered that the differences were “definitely” significant without having cal-
335 culated them, considered that seven was “evidently” not significantly different
336 from 7.6. However this argument depends on their estimation of the upper
337 bound of the standard deviation (“less than 1”, according to the authors). A
338 final remark is that, if we carefully check the calculations, we unfortunately
339 come to the conclusion that the first intuitive argument is correct, and that
340 the revised argument is not. It is sad to note that the willingness of Sturtevant
341 to contradict his own result was itself a scientific error, because in fact the first
342 better reflected the data, according to his own criteria.

343 It is striking that to this day, we know of no better technique to calcu-
344 late these numbers. Only the improved performance of computers allows the
345 present day researchers to enumerate all permutations and their inversion dis-
346 tances (for up to 13 genes in 1995 (Galvão and Dias, 2015)¹⁰ instead of up
347 to six in 1941). An asymptotic bound for the mean has been proposed (Bafna
348 and Pevzner, 1996) but it is not applicable to such small values. Consequently
349 I have used the enumeration method to compute, with modern techniques and
350 knowledge, the values for the numbers considered by Novitski, Sturtevant and
351 Ward¹¹. I consider these values more accurate than theirs, because I used a
352 complete enumeration of the space instead of an extrapolation. Of course these
353 values are the result of my own understanding of the problem and I cannot

¹⁰ It is a coincidence that the maximum number found in 1995 is precisely the one that biologists struggled with in 1937. That we have not been able to greatly improve our handling of the data is indicative of the inherent computational complexity of the problem.

¹¹ Note that the corrected values given here were obtained only with the published data and the statistical test proposed by the original authors. However this analysis requires computational tools that were not available at the time. There would probably be a lot more to discover if we were to redo this analysis with new data.

Evidently the two species are not more alike than could easily result from chance alone.

TABLE 4
Comparison of the required and calculated numbers of inversions to change the *melanogaster* into the *pseudoobscura* sequences.

ELEMENT	A	B	C	D	E	TOTAL
Loci	13	6	6	6	7	
Inversions required	7	2	4	3	3	19
Inversions calculated	7.6	3.0	3.0	3.0	3.7	20.3

Fig. 4 Excerpt from Sturtevant and Novitski (1941). The letters A, B, C, D and E in the table columns represent the chromosomes and correspond to X, IIL, IIR, IIIL, IIIR, respectively, in Figure 3. The row “Loci” shows the number of genes on each chromosome (corresponding to the number of letters in Figure 3). The row “Inversions required” shows the calculated inversion distances (on the observed arrangements). The row “Inversions calculated” shows the mean inversion distance computed from complete enumeration of permutations, or from samples of permutations, or from interpolation (this is the expected value on random arrangements). A modern calculation finds that all numbers are correct except 7 and 7.6 in column A (and their associated totals), which should be 6 and 7.9. The (wrong) conclusion, which could have been different with the correct numbers, is reprinted above the table. Reproduced with the kind permission of the *Genetics Society of America* and the journal *Genetics*.

354 discard the hypothesis that a future work will refute them. However I believe
 355 this is the best that can be achieved with our current knowledge and tech-
 356 nology. This analysis gives an expected inversion distance of 7.9 for 13 genes
 357 instead of the interpolated value of 7.6 from 1941 (see Figure 4). The standard
 358 deviation is 0.85 instead of the “less than one” estimation from 1941. This is
 359 not a big difference, but put end to end, all inaccuracies eventually change the
 360 conclusion.

361 2.6 When the progression of quantification leads to a succession of errors

362 To recap, there are three small errors or approximations in the 1937 and 1941
 363 articles: the minimum number of inversions (seven required instead of six), the
 364 expected number (7.6 instead of 7.9) and the standard deviation (“less than
 365 1” instead of 0.85). Taken together, these change the conclusion. With the
 366 corrected calculations, six inversions would have been considered significantly
 367 different from 7.9, falling outside the 0.85 standard deviation interval¹².

¹² A *bona fide* statistical test in this case would require a p-value rather than standard deviations. This was not considered in the 1937 and 1941 articles but it is possible to compute an empirical p-value from a sample of 1,000 uniformly sampled random permutations. This gives a probability of achieving six or less inversions for 13 genes of 0.06, a probability of achieving two or less inversions for six genes of 0.2, and a probability of achieving three or less inversions for seven genes of 0.35. Considering each chromosome independently is hardly conclusive. When all chromosomes are taken into account, gene inversions can be

368 It is retrospectively mind-boggling that Sturtevant and Novitski (1941), as-
369 sisted by a mathematician, claimed in 1941 to correct the statement of Sturte-
370 vant and Tan (1937), while in actual fact they were confirming the only wrong
371 statement of the earlier article, and introduced another error. In 1937 the
372 authors were cautious about the inversion distance number they found, but
373 in 1941 they noted that “this revision does not change the number of inver-
374 sions required to transform one sequence into the other”, thus retaining the
375 erroneous number and ignoring their initial reservations. The help of a math-
376 ematician, which ordinarily would have been considered a good idea for such
377 a problem, has perhaps been disastrous in this case, as it undermined, for the
378 wrong reasons, the sound intuitions that the biologists initially had.

379 Detecting these errors is not just a mathematical exercise or driven by
380 exaggerated attention to detail. It can have historical significance. Success
381 stories are more frequently reported than errors, but sometimes the path
382 taken by scientific research can be influenced by mistakes of different kinds
383 (Firestein, 2015; Livio, 2014). Here, the fact that closely related species, such
384 as *melanogaster* and *pseudoobscura* seemed to have no detectable similarity
385 in gene order may have contributed to orienting genetic research in other di-
386 rections. Indeed, this conclusion meant that a *Drosophila* phylogeny based on
387 chromosomes was hardly conceivable.

388 Not much changed after 1941. In a 50-page landmark article on the phy-
389 logeny of the *Drosophila* genus, Sturtevant (1942) devoted only two pages to
390 chromosomes and derived no decisive phylogenetic information from them. The
391 article mainly describes comparisons of morphological characters. By contrast,
392 in their book, Babcock and Stebbins (1938) recognized that chromosomes
393 could be used for reconstructing the phylogeny and evolutionary history of
394 the *Crepis* genus, even though *Crepis* is biologically more complex because
395 of the prevalence of hybridization and the diversity of reproductive modes in
396 plants. Babcock began his research on *Crepis* hoping it would be the plant
397 equivalent *Drosophila*, and to explore to what extent the results from Mor-
398 gan’s fly laboratory were generalizable (Smocovitis, 2009). He did not fully
399 succeed in this precise goal but in some aspects went beyond the research in
400 evolutionary genetics and cytology that was carried out on *Drosophila* species.

401 2.7 Epilogue

402 Of course the evolutionary genetics project started by Metz and Sturtevant
403 in 1914 did not stop because of a few mathematical errors that were made
404 in the 1930s and 1940s. One important challenge of their project was that it
405 necessitated a prohibitive amount of work to assess the homology of genes and
406 chromosome segments. In the articles analysed here (Sturtevant and Tan, 1937;
407 Sturtevant and Novitski, 1941), a catalog of homologous genes was compiled
408 based on similarities in phenotypic variation. This tedious method, which is

considered significantly different from what would be expected at random based on the usual significance thresholds.

409 difficult to automate, could not be envisaged beyond a certain evolutionary
410 depth.

411 The technique invented by Theophilus Painter (Painter, 1933, 1934) to de-
412 tect homologies between polytene chromosomes was exploited by geneticists
413 and cytologists within a comparative and evolutionary framework (Gannett
414 and Greisemer, 2004). At Caltech, it was used by Theodosius Dobzhansky,
415 first in association with Sturtevant and then independently after their part-
416 nership ended. Dobzhansky collected many *pseudoobscura* strains from all over
417 the United States, while Sturtevant collected what he felt was interesting for
418 genetics and, in particular, for his long-standing project of comparing chro-
419 mosomes from an evolutionary perspective. In 1936, they published together
420 the first phylogenetic tree based on chromosomal inversions (Sturtevant and
421 Dobzhansky, 1936) (see Figure 5).

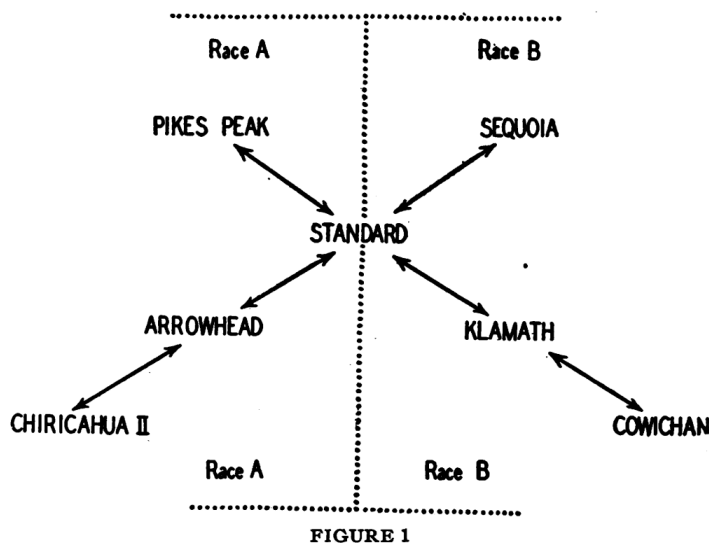


Fig. 5 A phylogeny of seven *Drosophila pseudoobscura* strains, from Sturtevant and Dobzhansky (1936). Reproduced with the tacit permission of the *National Academy of Science* of the United States of America.

422 Compared to building genetic maps, assessing homology using the cytolo-
423 gy of polytene chromosomes was fast and much less costly, which partly ex-
424 plains its immediate and long-lasting success. However, for studying evolution
425 over longer timescales, it was also somewhat limited. If there were more than
426 three overlapping inversions on the same chromosome, the technique yielded
427 almost no interpretable observations. Knowledge of all intermediary steps
428 was required. Nevertheless Dobzhansky and Powell (1975) followed by others
429 (Carson and Kaneshiro, 1976) finally reconstructed a phylogeny of *Drosophila*
430 species with more than one hundred arrangements and several hundred inver-

431 sions. Polytene chromosomes are still used to compare insects, and cytology
432 has morphed into cytogenetics, with extremely productive results Carson and
433 Kaneshiro (1976); Brehm (1990); Dutrillaux and Dutrillaux (2012). The prob-
434 lem of computing the inversion distance re-appears in some of these works,
435 alongside with *ad-hoc* solutions Brehm (1990).

436 From the 1960s onward, it became possible to identify homologies between
437 more distantly related organisms from sequence data. It was only in 1982,
438 probably driven by the availability of genomic sequences, that the inversion
439 problem was redefined in mathematical terms Watterson et al. (1982), without
440 any reference to Sturtevant's papers. This time, this work inspired a long series
441 of mathematical and computational studies Fertin et al. (2009).

442 3 Discussion

443 In this section three different aspects of the mathematical component of this
444 historical work are discussed more in depth. First, the type of mathematics
445 required to count inversions is discussed, in the context of a general mathema-
446 tization of science. It involved the design of algorithms, in particular combina-
447 torial algorithms, which were seldom used by evolutionary biologists, and even
448 by mathematicians. Second, the role of errors in this history and in science
449 in general is discussed. It is striking that the progressive quantification of the
450 question, which aimed to reduce the part left to intuition, and consequently
451 reduce the chance of errors, has in this case been the engine of errors. Third,
452 in searching for the causes of these errors, a special mention needs to be made
453 regarding the computational complexity of these mathematical problems. This
454 illustrates the underestimated influence of intractability in some biology re-
455 search programs.

456 3.1 Counting mutations as a computational biology problem

457 The introduction of measures, quantification methods, statistics and mathe-
458 matics into evolutionary biology and phylogeny traversed the twentieth cen-
459 tury (Hagen, 2003; Sommer, 2008; Suárez-Díaz and Anaya-Muñoz, 2008; Suárez-
460 Díaz, 2010). This tendency is visible in biology, science and society in general
461 (Kay, 1993; de Chadarevian and Kamminga, 1998; Porter, 1996). Several re-
462 searchers saw this as a possibility to turn phylogeny into a *bona fide* science.

463 Computing evolutionary distances has been an important activity for es-
464 tablishing phylogenetic relationships. In the first half of the twentieth cen-
465 tury this was done for example with serological and immunological reactions
466 (de Chadarevian, 1996; Strasser, 2010b; Hagen, 2010), and later on with DNA
467 hybridization (Suárez-Díaz, 2014). Biologists hoped that results would reflect
468 the amount of divergence between proteins or chromosomes.

469 With the advent of molecular biology in the 1960s, discrete DNA mutations
470 could be directly quantified (Hagen, 1999, 2003, 2010; Strasser, 2010b; Suárez-
471 Díaz, 2014; Dietrich, 1994, 1998; Morgan, 1998; Sommer, 2008), with the use

472 of a particular type of mathematics, often aided by computers (Hagen, 2000,
473 2001; Strasser, 2010a).

474 The kind of mathematics used by Sturtevant for counting inversions is
475 unusual in this regard. On the one hand, successive mutations in semantic
476 characters were counted, in the same way that substitutions in protein or
477 gene sequences are counted. In that sense, it is closer to the mathematics
478 developed in the 1960s than to the quantifications performed in the 1930s,
479 which was developed as a proxy, *i.e.* “waiting for sequences” (Hagen, 2010).
480 On the other hand, there is a crucial difference between counting inversions
481 and counting point mutations in sequences: as an approximation, the different
482 sites of a sequence subject to point mutations can be considered independent
483 from each other, while with overlapping inversions, gene arrangements are
484 inaccessible to this simplifying hypothesis. These two aspects give a special
485 status to this mathematical problem, and explain why counting inversions,
486 although it precedes counting point mutations by 30 years, is still much less
487 developed.

488 The technique for counting inversions involves the design of an algorithm.
489 There is no known mathematical formula for estimating the inversion distance.
490 The only way to calculate the inversion distance is to apply successive inver-
491 sions to the permutation in order to come closer, one step at a time, to the
492 alphabetical order. Sturtevant, his students and perhaps Ward, even if it is not
493 specified in the publications, must have applied this type of method. As they
494 proceeded to calculate the inversion distance for hundreds of permutations,
495 they must have formalized a method. Indeed, not only did they perform the
496 calculations for the permutations stemming from their biological data, but also
497 from the complete set of permutations for up to 6 genes (720 permutations),
498 plus a sample of dozens of permutations of seven to nine genes. They do not
499 describe how they carried this out but admit their method had limits “For
500 numbers of loci above nine the determination of this minimum number proved
501 too laborious, and too uncertain, to be carried out” (Sturtevant and Novitski,
502 1941). This means that they were certain for permutations with up to nine
503 loci, which is already, for some of them, a difficult exercise. We do not know
504 how they came up with this confidence but we can only imagine they used an
505 automatic method, *i.e.* an algorithm.

506 Algorithms have been used by mathematicians for a long time and were
507 known to biologists. However their use as mathematical objects was not formal-
508 ized and few mathematicians were specialized in designing algorithms. Turing’s
509 famous articles were published at the time when Sturtevant was carrying out
510 his research (Turing, 1936). This absence of a constituted field with its own
511 practices and applications explains why, despite having constructed an algo-
512 rithm to solve the inversion problem on dozens of permutations, Sturtevant,
513 Tan and Novitski did not even bother to describe it, even if it must have been
514 a considerable endeavor.

515 Moreover, almost all algorithms known at the time were algorithms on
516 continuous algebraic structures, allowing for example independence between
517 dimensions and working with one dimension at a time (think of Gaussian elim-

518 ination for inverting a matrix, Euclid's algorithm for computing the greatest
519 common divisor, or Fisher's Anova). The design of algorithms on combinato-
520 rial structures like permutations or graphs was developed in the second part
521 of the 20th century (the description of finding the shortest path in a graph
522 dates back to 1956).

523 Modern data has not changed this problem much. Even if the possibility of
524 analyzing DNA sequences at the level of the entire chromosome has brought
525 more data, more precision and more evolutionary depth, the principle behind
526 chromosome comparison, unlike the detection of point mutations in genes, has
527 not changed with the availability of sequences and still consists in counting
528 inversions (Pevzner and Tesler, 2003; Murphy et al., 2005). Nevertheless re-
529 cent developments have been numerous and gave rise to many variants of this
530 problem. For example the possibility of knowing the reading direction of genes
531 has unexpectedly decreased, to a small extent, algorithmic difficulties (Fertin
532 et al., 2009).

533 To conclude this part by an anecdote, it is ironic that what we today
534 consider a computational biology problem originates from the laboratory of
535 Thomas Hunt Morgan, who allegedly had an aversion to computers. It is said
536 that he banned Friden calculators from the biology department at Caltech,
537 because he mistrusted all quantitative and automatic results¹³. If this attitude
538 seems to run counter to history, the present narrative, made up of errors
539 introduced at the same rhythm as the quantification, does not entirely prove
540 him wrong.

541 3.2 The importance of errors

542 It is almost epistemologically impossible to retrace the history of an error. To
543 present the genesis of knowledge while specifying that it is erroneous is already
544 seeing it through the eyes of a subsequent event, that of its falsification. Writing
545 about an error is in itself an anachronism.

546 On the other hand, placing errors on an equal footing as currently ac-
547 cepted knowledge, without specifying that they have been refuted, also poses
548 an epistemological difficulty. The possibility of studying the history of science
549 without disentangling what is the true from what is the false, according to a
550 current view, is subject to debate Chabot (1999).

551 This could explain why histories of scientific errors are scarce (Firestein,
552 2015; Livio, 2014). Errors are often used for educational purposes (Bosch,
553 2018), to explain how not to make them. Or they can be a way to celebrate
554 the discovery of the truth, by contrast. At best, scientific activity can be seen
555 as a constant effort to track errors Popper (1959).

556 Nevertheless errors might also be a part, perhaps a major part, of scientific
557 activity. The production of errors, and not their falsification, can be an inter-
558 esting process. It is all the more interesting when considering the example

¹³ This story is attributed to Charlie Munger in Belevin (2007).

559 described in this article, because the errors appeared and accumulated pre-
560 cisely at a time when quantification progressed, and probably were the result
561 of quantification. Because we usually consider quantification as a process that
562 reduces the possibility of errors resulting from subjectivity and intuition, it is
563 remarkable that in this case the result was the opposite.

564 Let me remind the reader how, in this example, the accumulation of small
565 errors have been led to a wrong conclusion. First in 1937 Sturtevant and Tan
566 stated that the observed inversion distance of the gene arrangement on the X
567 chromosome of *Drosophila* species was 7. At the time this was not an error
568 because the authors were aware that this number could be 6, even if they did
569 not find a scenario with 6 inversions. In 1941 Sturtevant and Novitski, with
570 the help of Ward, confirmed the number 7 (error number one) and compared it
571 with the expected inversion distance from random arrangements, calculated as
572 7.6, when the correct value is closer to 7.9. This value should not be considered
573 as an error because it is the result of an interpolation and was not claimed to
574 be the real value. However this value was compared to the observed inversion
575 distance of 7, which falls into a standard deviation interval of "less than one" if
576 centered on the expected value of 7.6. When considering the correct values, we
577 come to the opposite conclusion: 6 does not fall within the standard deviation
578 interval (0.85) centered on 7.9.

579 Therefore the error number two is to use approximate quantification, know-
580 ing but forgetting that they are approximations, to draw a conclusion from
581 the statistical test. The robustness of the biological conclusion is not tested
582 for the three approximations (approximation of the inversion distance, linear
583 interpolation of the expected value, and upper bound of the standard devia-
584 tion). In this case, the result with less quantification (the result from 1937)
585 is closer to what can be concluded from the data than the result with more
586 quantification (the result from 1941).

587 We might wonder how enlisting the help of a professional mathematician
588 has had such a disastrous impact on the computations. In all probability Ward
589 concentrated on what he knew best, *i.e.* statistics (computing an expectation
590 and a standard deviation from a sample), and focused less on the problem that
591 he —like everyone else— had no clue about, namely the computation of the
592 inversion distance.

593 The addition of errors in the second publication is explained by the type
594 of mathematics that we now know to be useful to handle the problem, which
595 was unknown at the time. However the mathematics of counting inversions has
596 hardly improved, because of the intrinsic difficulty of the problem, that is, its
597 computational complexity. This intrinsic difficulty could account in part for
598 this accumulation of errors, and might explain, more generally, the trajectory
599 of some biological research programs.

3.3 The importance of computational complexity

The errors I have reported were obviously not the result of incompetence or poor intuition on the part of scientists involved. They could be due to a lack of real interest in the problem from their part. Indeed, assessing gene homology using genetic techniques was time-consuming, costly, and could not be automated or generalized to more distant species. This meant that large-scale research programs based on this technique had little chance of success. This may explain why the results of the comparison between *melanogaster* and *pseudoobscura* have not been reproduced for other species, and why the mathematical techniques have not been refined and the errors not corrected by additional work.

However several facts tend to contradict the idea that there was a lack of interest from the part of Sturtevant. Sturtevant requested the help of a professional mathematician despite being himself a decent amateur mathematician. Two publications, with two different Ph.D. students, published four years apart, mention the mathematical problem. In the latter, intuitive statements are abandoned for quantified statements. A supposed error in the first publication is corrected in the second. These facts suggest that Sturtevant was reasonably interested in obtaining the right answer to the problems he raised.

One of the reasons why he did not achieve this right answer at the time could be that the mathematical problem raised by successive overlapping inversions is intractable¹⁴. These problems contain an inherent provably difficulty which prevents the mathematical construction of any tractable solution¹⁵. Although biologists are often not aware of computational complexity, or do not consider it important, it is a constraint that can influence the direction of biological researches. The example given here illustrates the influence of such a constraint. Today computational sequence alignment tools detect point mutations but not inversions. This is due to the computational complexity of detecting inversions and not to an absence of inversions. In that case computational complexity could explain why some biological processes are extensively studied while others are much less quantified.

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¹⁴ Note that this contrasts with the history of protein sequence alignment, where it became possible to compare two related sequences without excessive mathematical involvement (see, for example, (Margoliash, 1963)). I am not saying that sequence alignment did not pose an interesting mathematical problem but it was inherently easier to solve with the intuitive ideas of biologists than computing an inversion distance.

¹⁵ Finding the minimum number of inversions to transform a sequence of letters into alphabetical order is provably intractable (Caprara and Lancia, 2000).

636 anonymous historians who have kindly helped me improve the historical as-
637 pects of this article, find the relevant secondary literature and get rid of most
638 teleological and anachronistic arguments.

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