# At the dawn of chronobiology

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Jean-Jacques d'Ortous, squire and lord of Mairan (1678–1771), was at the time a member of the Royal Academy of Sciences, where his official title was "*pensionnaire-géomètre*". Yet Mairan did not himself present his paper on botanical observations (*Observation botanique*, 1729) to the Academy.[1] Did this mean that he lacked interest in his own discovery? Probably not, for this has always been a very common academic practice, especially in eras when travelling was difficult and time-consuming. This paper was indeed judged worthy of (albeit brief) mention in his eulogy[2] – a point I will return to below – alongside his contributions to "experimental physics and natural history". What is less common is that this discovery, which was made almost three centuries ago, is still cited in scientific texts, including specialist articles. Indeed, most specialists consider it the first genuine publication, if not the founding publication, in their field, that is to say chronobiology – which emerged only at a much later date.[3] I imagine that M. de Mairan would be most surprised to learn of the posthumous success enjoyed by this ostensibly unassuming piece of work.

In what follows, I will go through Mairan's paper step by step, with the aim of explaining both the modern-day notions and issues that underpin it and a few later experiments that honed and developed his work. I will also attempt to briefly outline the context in which Mairan worked, drawing on his subjects of predilection as they are described in his eulogy and the most accessible parts of his copious correspondence with other scientific minds of the day.

1. The presentation was probably delivered by Jean Marchant (~1650–1738), the academician who read the descriptions of the three plants mentioned on the following page.
2. Delivered by Jean-Paul Grandjean de Fouchy, M. de Mairan's successor as permanent secretary (*Hist. de l'Acad. Royale des Sciences*, 1771, 89–104; cf. p.100). All unreferenced quotations not from the analysed text are from this eulogy.
3. In the bibliographic database *PubMed*, the first reference that uses the word "chronobiology" to describe this scientific field dates from 1967.


***Figure 1:* Jean-Jacques d'Ortous de Mairan (1678–1771).** *Portait by Louis Tocque (1696–1772), engraving by Pierre-Charles Ingouf (1746–1800). (Dibner Library of the History of Science and Technology, Smithsonian Institute).*

*We know that the Sensitive-plant is heliotrope, that is to say that its branches & leaves always turn in the direction of where there is most light, & we know that in addition to this property, which it shares with other Plants, it has another, special one…*

It is difficult to say for certain which plant species M. de Mairan had observed, for, prior to the first edition (1735) of the *Systema Naturae* by the famous Swedish naturalist Carl Linnaeus (1707–1778), Mairan was not able to identify it with any accuracy. What follows is the definition provided in the dictionary of the Académie française in its 1694 edition: "Species of plant, so called because it seems possessed of feelings, & shies away from touch." When the botanist Augustin-Pyramus de Candolle (1778–1841), originally from Geneva, described his experiments at the Jardin des Plantes in Paris in the early 19th century, he was careful to identify the Sensitive-plant using the Linnaean Latin classification. The plant was given the evocative name of *Mimosa pudica*...

***Figure 2:*** **Mimosa pudica*, or Sensitive-plant.***

The "distinctive" feature described in the 1729 text, and which earned the plant its name, is that it is

*sensitive to the Sun and daylight: the leaves & their peduncles fold themselves away & contract around sunset, in the same way they do when the Plant is touched or shaken.*

In reality, regular daily movements of this kind, taking place at practically the same time every day, are quite common in the plant world. This is acknowledged at the start of the second paragraph, which mentions

*other Plants, whose leaves or flowers open in the day, & close at night.*

Candolle described these leaf movements as "plant sleep". It was an insight that captured the attention of fellow scientists by suggesting a potential link – indeed a stronger one than they probably realised – with the daily rhythms of the animal world. This "sleep" would later be studied in many plant species, in particular by the German botanist and physiologist Wilhelm Pfeffer (1845–1920).[4] Linnaeus himself had noticed that the flowers of different plant species open (and close) at different times of the day, and not necessarily at sunrise (and sunset). Indeed, he had even designed a flower clock: a circular flowerbed with plant species arranged according to the moment of the day when their petals spread open, thereby telling the time.


***Figure 3:* A flower clock (**Blumen-Uhr***), as imagined and described (species by species[5]) by Linnaeus in 1751.***

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4. The German term for this phenomenon is *Schlafbewegungen*, literally "sleep movements" (which is also the term used in English).
5. Linnaeus's description can be found on Wikipedia.

*But M. de Mairan observed that for this phenomenon to take place, it is not necessary for [the plant] to be in the Sun or outdoors. It is simply a little less pronounced when [the plant] is always kept in a dark place. [The plant] still opens up quite perceptibly during the day, & folds away or closes for the night at the same time every evening. The experiment was performed towards the end of summer, & repeated several times.*

The modern-day scientist knows how important it is to be able to reproduce an experiment, but this requirement was not necessarily self-evident in Mairan's day. The order in which it is presented may come as a surprise, though, as the conclusion precedes the – somewhat elliptical – description of the experiment itself! But the gist of the matter is summed up in a single sentence: the leaves' rhythm – this is not the term used – persists despite their lack of perception of night and day. This persistence is *the* hallmark of what, from the 1960s onwards, would be known as **circadian rhythms**, from the Latin *circa* (around) and *diem* (day). Such rhythms can be contrasted with **nycthemeral rhythms**, a term derived from the Greek, which take place only when day and night alternate over a **period** of 24 hours, and cease if the alternation stops. One example is the heliotropism mentioned by Mairan: it is a direct result of sunlight, and ceases in conditions of constant darkness.

Candolle was the first to show that when plants are deprived of natural light, their "plant sleep" follows a circadian, rather than an exactly 24-hour, rhythm. In addition, when he exposed his *Mimosa pudica* to constant light instead of leaving them in uninterrupted darkness, he observed that while the leaf movements continued, they did so over a period shortened by one and a half to two hours. Pfeffer, who no doubt bequeathed us the heftiest tome on the subject,[6] performed experiments on many plant species, thereby confirming beyond a shadow of doubt that leaf movements are not simply a corollary of the earth's rotation: the movements are not performed in an exactly 24-hour period, and indeed vary from species to species.

Mairan nevertheless conceded that the leaf movements of his Sensitive-plant were slightly less pronounced when the plant was placed in constant darkness, or at least semi-darkness. Twentieth-century chronobiologists would describe these conditions as DD (dark-dark) – compared to LD (light-dark) – cycles. Though a circadian rhythm must persist (by definition) in DD, it does not

6. 154 pages, soberly titled *Contributions to knowledge of the formation of leaf movements*, published in 1915 in the *Papers of the Mathematics–Physics Section of the Royal Academy of Sciences of Saxony* (in German).

generally have the same characteristics as in LD. The amplitude may be more pronounced in LD than in DD, but that is beside the point: the cyclical variations in light determine **the phase** of the biological rhythm in question. In other words, they **synchronise** the rhythm, by determining not only its period[7] but also at what time it will reach its extreme values (the maximum opening and closing of the leaves, in the case of leaf movements). This is exactly what Mairan suggests in the following passage:

> *It would be curious to test […] whether, using kilns heated to higher or lower temperatures, one could artificially recreate a day & night perceptible to [plants]; and whether in doing so one could reverse the order of the phenomena of true day & true night.*

The advent of electricity has enabled chronobiologists in the 20th and 21st centuries to submit their experimental subjects to a wide variety of light/dark and hot/cold cycles, or even to combine the two types of cycle if they so wish. Thus it has been shown that in order to stay attuned to the passing of the seasons, most living organisms, whether animals or plants, rely on the relative length of the day[8] or night during 24-hour daily cycles. Though a discussion of these experiments is beyond the scope of this paper, they have significant practical consequences, enabling arable and livestock farmers to bring a crop into flower or reproduce a species in almost any season, simply by exposing them to artificial dark/night cycles that imitate those of the desired season.

If Mairan suggested using reversed hot/cold cycles rather than reversed day/night cycles, it is probably because he had doubts as to whether he could maintain adequate artificial lighting throughout the whole night. The fact that circadian rhythms are acutely sensitive to light, which would not be fully proved until the beginning of the 21st century, suggests that his pessimism was unwarranted, and that the light of a single candle may have sufficed.

Yet Mairan's pessimism gave him the interesting idea that nycthemeral variations in temperature, as well as in light, could synchronise circadian rhythms. He was right. Indeed, though we know a good deal less about the action of temperature compared to that of light, these two cyclical environmental factors are considered the main "time givers"[9] in circadian rhythms. The

7. So, 24 hours exactly in the case of natural day/night cycles. In laboratories, scientists can "force" oscillations of different periods within so-called "entrainment limits", just as they can with physical oscillators.
8. Known as a photophase or photoperiod, hence the term photoperiodism, which describes this seasonal physiological reaction to changes in the length of the day.
9. The original German term is *Zeitgeber*.

sensitivity of circadian rhythms to temperature cycles, even weak-amplitude cycles, is at the origin of the potentially most serious criticism levelled at Mairan, namely that no matter how protected from daylight his Sensitive-plant may have been, it could still have been exposed to temperature variations between day and night. If this were the case, it is argued, these temperature variations would have caused the persistence of the leaf movements.[10] Unless the thick walls of his manor house kept the rooms air-conditioned, that is… It is surprising that Mairan does not discuss this point, especially as he suggests using temperature cycles to synchronise leaf movements.

This was one of several reasons why Henri-Louis Duhamel du Monceau (1700–1782) repeated Mairan's experiments in 1758. He went as far as installing his plants in a deep wine cellar where the temperature was very stable and absolutely no sunlight could penetrate, or even in large leather trunks wrapped in blankets. The plants' leaf movements continued, despite the fact that they were far more effectively cut off from daylight.

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And what about endothermic organisms – so-called "warm-blooded" birds and mammals – whose central temperature, unlike that of plants and other animals, is virtually independent of the ambient temperature? In fact, independence does not spell constancy, as our internal body temperature itself follows a circadian rhythm,[11] reaching its lowest point in the middle of the night and rising in the evening to values a few tenths of a degree Celsius higher than when one wakes up. It even turns out that these slight variations are able to synchronise other circadian rhythms within the organism! This leads us to one last chronobiological concept, and one that is crucial but entirely absent from Mairan's nevertheless highly important work. This is the concept of the **circadian clock**. From an experimental point of view, his article therefore asks a very pertinent question. It adduces a correct observation (notwithstanding the minor issue of temperature control), and one that seems to answer the question at hand. But, in the absence of a conceptual framework capable of elucidating its

10. Temperature cycles with an amplitude of one or two degrees are enough to synchronise the circadian rhythms of most species.
11. Considered to be the first circadian rhythm described in humans. "That unfortunate delicacy of many Invalids, who perceive the difference between day & night from their sickbeds" might suggest the (now acknowledged) influence of **internal** rhythms on the course of a disease. However, here Mairan is simply referring to subtle **external** influences that were identified only by confining patients to wards cut off from daylight, or by their heightened sensitivity to such influences.

true significance, it remained just that: an observation. In other words, it would remain mere observation just as long as the question was not formulated quite right – or, if you prefer, it was not asked for the right reasons.

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*The Sensitive-plant senses the Sun without ever seeing it.*

This interpretation of Mairan's study seems to go without saying. It is repeated in his eulogy, which, amid a long list of his studies, mentions "his observation of the Sensitive-plant, which appears to sense the action of the Sun & daylight, even when not exposed to them". Many a scientist would continue to reason in these terms over the next two centuries, doggedly continuing their pursuit of a hypothetical "X factor" connected to the earth's rotation and apparently capable of exerting its influence on living organisms that "[n]ever [see] it". Yet the observations of Messrs de Candolle and Pfeffer, and those of many others, surely show how difficult it is to explain such rhythms by the "action of the sun", for they do not keep the same time.

Without going into the details of this controversy – which did not die down until the 1970s[12] – let's consider a possible epistemological obstacle to its resolution: the difficulty in imagining a biological mechanism capable of maintaining such regular rhythms over such a long period of time (relative to common biochemical processes), i.e. over days, weeks or even months. The eventual discovery of such mechanisms within plant, animal and even bacterial cells finally put an end to this debate. These mechanisms operate veritable biological clocks within the cells, regulating the rhythm of cell life, the functioning of tissues and the behaviour of organisms. Present in all organs, they are endowed with a degree of autonomy, and interconnected so as to ensure an overall physiological coordination in harmony with day/night cycles. When we travel across several time zones during transmeridian flights, these mechanisms are thrown into cacophonous disarray, and the result is jet lag.

**The biological clock in mammals**

The molecular mechanisms of the circadian clock, or at least one of its essential aspects, can be usefully imagined as a negative feedback loop. In this loop, activation alternates with inhibition. The latter is triggered by the former, and vice versa. At daybreak, one set of factors

12. See "La controverse des horloges biologiques", A. Klarsfeld, *La Recherche*, no. 351, 44–47 (2002).

activates a second group, which in turn gradually inhibits the action of the first. At nightfall, the concentration of negative factors diminishes because the expression of these factors is no longer activated. Positive factors become progressively less inhibited and a new cycle begins. In mammals, the positive factors are two proteins: the transcription factors CLOCK (abbreviated as CLK) and BMAL1.[13] The negative factors are also proteins: PERIOD (abbreviated as PER) and CRYPTOCHROME (abbreviated as CRY).

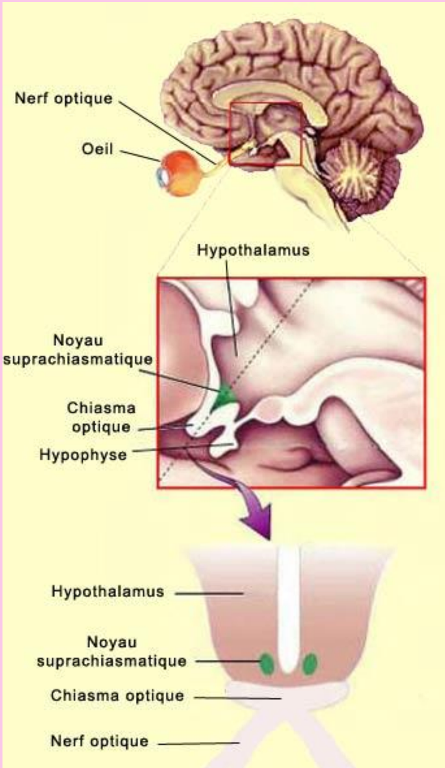


***Figure 4:* The suprachiasmatic nucleus in humans** *(image: McGill University, Montreal). This is where the central biological clock in mammals is found. Measuring about 0.5 x 1 mm and containing around 10,000 cells, it is situated in the hypothalamus, just above the optic chiasm. It synchronises so-called "peripheral" clocks in the other organs. Each clock uses practically the same molecular apparatus.*

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*But the ordinary occupations of M. Mairan prevented his pursuing his experiments to this point, & and he contented himself with a simple invitation to Botanists & Physicists, who themselves might have other matters to pursue. The course of true Physics, which is Experimental, can only ever be exceedingly slow.*

13. Abbreviation of "brain and muscle Arnt-like protein-1".

The concluding words of the article are surprisingly sober, though visionary.[14] Only in the mid 20th century was the *Observation botanique* of 1729 recognised as evidence of an endogenous biological mechanism for measuring time, and it took a few more decades to identify this mechanism and pinpoint its workings. The "invitation to Botanists & Physicists" was also prophetic. As if wishing to celebrate the *Observation*'s bicentenary, in 1928 the Institute for the Study of the Physical Bases of Medicine at Frankfurt University recruited two young German botanists (Erwin Bünning and Kurt Stern) in an effort to shed light on the nature of the famous "X factor". Their experiments are considered classics in their field. In short, they revealed a previously unsuspected sensitivity in plants to the red light used in laboratories. Rather ironically, red light had been used because it was (wrongly) thought to prevent disturbances in the plants' rhythms! Today, chronobiology is indeed a fundamentally pluridisciplinary research area, bringing together geneticists, biochemists, botanists, zoologists, neurobiologists, agronomists, physicists, mathematicians, psychologists, doctors, etc.

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To conclude, I would like to return to M. de Mairan's "ordinary occupations" (which "prevented his pursuing his experiments" into the Sensitive-plant in greater depth). To my mind, their number and range seem rather out of the ordinary. Mairan – who as early as 1736 was described by Voltaire as one of the five most remarkable scholars of the 18th century[15] – wrote a great many articles and treatises. A number of these attracted considerable attention, such as his *Traité physique et historique de l'aurore boréale* (*Physical and Historical Treatise on the Aurora Borealis*), a publication he worked on in the same period as his *Observation botanique*.[16] He was one of the first to interpret this impressive riot of colours as a cosmic phenomenon associated with sunspots, rather than as an atmospheric one. Prior to this, he had been commended three

14. During a seminar in February 1970, Colin Pittendrigh (1918–1996), one of the pioneers of modern chronobiology, is said to have exclaimed "How right he was!", cf. *The Living Clocks,* R. R. Ward (1971). This slowness is difficult for the general public to understand, partly because the history of science is often presented as a one of uninterrupted progress, with new discoveries following on the heels of earlier ones, and partly because the rhetoric of the media ("Immortality: just around the corner") and politicians ("Winning the war against cancer") is necessarily short-termist.

15. To the extent of describing him as the intellectual superior of M. de Fontenelle (1657–1757), whom M. de Mairan succeeded as permanent secretary to the Académie. "It seems to me", wrote Voltaire in 1769, "that M. de Mairan possesses in depth what M. de Fontenelle possessed in superficy".

16. The treatise was originally published in 1731. A revised and extended version was printed in Paris in 1754.

years in a row (1715–1717) by the Royal Academy of Sciences of Bordeaux: first for his *Essay on Barometric Variations*, then for his *Essay on Ice* – which was reprinted in Paris in 1730 and 1749 – and finally for his *Essay on the Cause of Light in Phosphorus and Noctiluca*. The Academy of Bordeaux then requested that he stop entering the competition: “but only by making him one of the very same Academicians who had thrice awarded him the prize. This honour & the manner in which it was conferred were worth a fourth prize.”

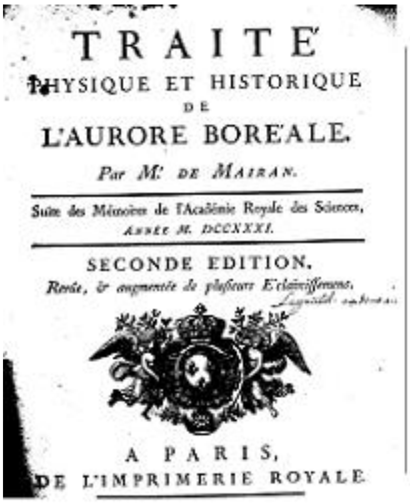
TRAITE
PHYSIQUE ET HISTORIQUE
DE
L'AURORE BOREALE.
Par M. DE MAIRAN.
Suite des Mémoires de l'Académie Royale des Sciences, Année M. DCCXXXI.
SECONDE EDITION.
Revûe, & augmentée de plusieurs Eclaircissemens.
A PARIS,
DE L'IMPRIMERIE ROYALE.

***Figure 5:*** ***(left)*** **Traité physique et historique de l’aurore boréale***, M. de Mairan, 1731* *(here the 2nd revised and expanded edition, 1754, Gallica);* ***(right) Aurora borealis near Belfort, 20 November 2003*** *(WikiCommons, author: Raymond Mercier).*

In each of these years he also sent a separate paper to the Royal Academy of Sciences in Paris. In addition to his three “triumphs” in Bordeaux, these papers inspired “a desire within the Academy [of Paris] to make him one of their own”. “The occasion presented itself in 1718, just after his arrival in Paris”, and he obtained “the position of Associate-“*géomètre*” […], without first being appointed to the rank of Assistant: clear proof of the esteem in which he was held at the Academy”.[17] In 1743, it was the turn of the Académie française to welcome him into its fold.

Mairan was a man of letters and corresponded with Malebranche, [18] notably, as well as with other illustrious contemporaries such as Voltaire and Mme du Châtelet. One study[19] of his exchanges with several Genevan scholars over a

17. “A few months later he was presented with another token of esteem. M. Rolle, now elderly and infirm, requested his retirement, which was granted. M. de Mairan, who had been received barely seven months earlier, was favoured over all his rivals, & chosen to replace him on 8 July 1718. The Academy deemed that great ability could compensate for the brief time he had been entitled to make use of it.”
18. Published for the first time in 1841 and again in 1947 (Librairie philosophique J. Vrin).
19. “Jean-Jacques Dortous de Mairan and the Geneva connection: scientific networking in the 18th century”, Ellen McNiven Hine, Voltaire Foundation, Oxford (1996).

period of half a century identifies at least 11 major themes: the shape of the Earth, the *aurora borealis*, light and sound, heat and cool, *vis viva* (living forces), electricity, machine-animals, monsters, chemical affinities, mathematics, and Newtonian natural philosophy. A number of these themes underlie his interest in leaf movements. These were, namely, distinguishing the straightforward influence of sunlight from a remote influence of another sort (for example, an electrical one: this in any case was the initial working hypothesis of Bünning and Stern, though it proved fruitless); using temperature variations to mimic the alternation of day and night; revealing the workings of animal-machines (although our discussion concerns plants, their movements are ostensibly what they have most in common with animals); or even seeking out other unstudied but more common sun effects besides the *aurora borealis*. Significantly, the incident that apparently incited him to write his *Traité physique et historique de l'aurore boréale* occurred in October 1726. It was "admirable, but […] instilled such fear into a large section of the population of this Kingdom" that the Academy was instructed to provide "an explanation to reassure minds by Saint Martin's Day". A fine example of the spirit of the Enlightenment if ever there was one…

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*(September 2013)*

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