Abstract  
After birth setting up an effective immune system is a major challenge for all living organisms. In this paper we show that this process can be explored by using the age-specific infant death rate as a kind of sensor. This is made possible because, as shown by the authors in Berrut et al. (2016), between birth and a critical age $t_c$, for all mammals the death rate decreases with age as an hyperbolic function. For humans $t_c$ is equal to 10 years. At some ages the hyperbolic fall displays spikes which, it is assumed, correspond to specific events in the organism’s response to exogenous factors. One of these spikes occurs 10 days after birth and there is another at the age of 300 days. It is shown that the first spike is related to viral infections whereas the second is related to bacterial diseases. By going back to former time periods during which infant mortality was much higher than currently, it is possible to get a magnified view of these peaks which in turn may give us useful information about how an organism adapts to new conditions. Apart from pathogens, the same methodology can be used to study the response to changes in other external conditions, e.g. supply of food, temperature or oxygen level.

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Introduction

Why did we entitle this note “Phenomenology of death rates”? In physics the word “phenomenology” refers to the interface between experimental results and theory. Its purpose is to bring together appropriate data and organize them in the best way for testing any existing predictions. When no theory is available the objective is to bring to light phenomenological regularities and to recommend further experiments to probe their validity.

In the social sciences such a program usually cannot be carried out because of limitations in the data available and the impossibility to produce new ones to fill the gaps.

Age-specific death rates by cause of death are probably the variables which come closest to the situation prevailing for physical data. There are two main reasons for that.

- Death records were the first demographic data to be collected in a systematic way. In the mid-19th century in all industrialized countries organizations were set up in order to record the age, date and cause of deaths. Recording first started in cities and was progressively extended to rural areas. In the case of the United States, the so-called “death registration area” covered about 40% of the population in 1900 and 96% in 1930.

- By the end of the 19th century medical authorities and statisticians from over all developed countries agreed on an international classification of the causes of death. The adoption of this classification was an essential step because it ensured cross country comparability.

The age-specific postnatal death rate follows a hyperbolic decrease $\mu_b(t) \sim 1/t^\gamma$ until a critical age $t_c$ after which it starts to increase; then, for most species, it keeps increasing until death. For humans, $t_c = 10$ years. This pattern holds, not only for the global (i.e. “all causes”) mortality but also for individual diseases, albeit with distinct values of $\gamma$. Fig. 1 illustrates this statement for the case of metabolic diseases. Why did we illustrate this pattern through metabolic disorders instead of a case that would be closer to the class of infectious diseases which will be considered later on in this paper? We wanted to emphasize that the strengthening (or weakening) of the immune system was not directly responsible for the hyperbolic fall (nor for the exponential growth). This does of course not mean that they do not affect death rates in any way but only that the basic pattern is due to another mechanism. A plausible mechanism is described in Appendix A.

In the present note we identify and study two deviations with respect to the hyper-
Fig. 1  **Death rate due to metabolic disorders, USA 1999-1984.** Included in this class of disorders are for instance intolerance to lactose and defects in the metabolism of carbohydrate. These down- and up-going curves ($\mu_b(t) \sim 1/t^\gamma$, $\mu(t) \sim \exp(-\alpha t)$ respectively) are similar to those for “all causes” death rates except that the exponents are not the same. For $\gamma$ it is 0.99 instead of 0.61 here. For the doubling time in the adult phase it is 8.6 years instead of 9.4 years here. $\gamma$ and the doubling time can be seen as signatures of a specific class of diseases. **Source:** CDC “Wonder” database 1999-2014 ([http://wonder.cdc.gov/ucd-icd10.html](http://wonder.cdc.gov/ucd-icd10.html)). The data are average annual death rates over the 16-year long interval 1999-2014.

We wish to see if the infant death rate can be used as a kind of spectrometer from which information can be derived about the complex mechanisms which lead to the regulation of the immune system.

To carry out this program the paper takes the following steps.

- First, we must identify the time intervals during which the system undergoes major transitions.
- Once transitions have been detected one must make sure, through comparative analysis, that they have a broad validity and are not just brought about by specific local conditions.
- The next step is to identify the factors through which these deviations can be explained. It will be seen that the first deviation is related to viral infections while the second is related to bacterial infections. There are good reasons to think that the second deviation is due to the transition from protection provided by maternal antibodies to the building up of an endogenous immune system. In its shape this bump is very similar to the one observed in fish during the transition from yolk sac feeding to feeding on exogenous sources of food. It seems that in both cases the transition brings about a fragility which results in the transient death rate peak that is observed.
Deviations from the hyperbolic law of infant mortality

Identification of the time intervals of the transitions

In Fig. 1 it can be seen that between 0 and 10 years the infant death rate decreases by several orders of magnitude. Without a vertical log-scale, the whole curve would be crushed and compressed against the x-axis. The log-scale makes the curves more readable but Fig. 2a still does not reveal any clear signal. In such a situation a common trick is to take the ratio of successive curves in order to filter out the huge variations. This is done in Fig. 2b for the case of Switzerland and the United States.

Fig. 2a,b  Death rates for all causes in Switzerland and the United States. (a) Death rates in Switzerland in successive decades. (b) Death rate ratios in Switzerland and the United States. The “ref” label corresponds to the rates for 1975-1978. Sources: Switzerland: Encyclopédie statistique de la Suisse. Statistique historique. Santé. Mortalité et causes de décès [Statistical Encyclopedia of Switzerland. Historical Statistics; section: Health, Mortality by causes of death.]; available on Internet at the following address: http://www.bfs.admin.ch/bfs/portal/fr/index/infothek/lexikon/lex2.html USA: Linder and Grove (1947, p. 574).

The death ratios reveal two peaks, one at 9 days and the other at 300 days after birth, which are common to the two countries. In addition the curves for Switzerland show a steady decrease in the amplitude of these peaks The fact that there are only few data points to cover the whole age interval means that the locations of 9 and 300 days are defined with substantial error bars which, however, are difficult to estimate precisely.

We can conclude this first experiment by saying that there are two indentations on the curves of the age-specific mortality from “all causes” which are present both in Switzerland and in the US. While not easy to identify on the rates themselves, they become clearly visible on the ratios of the death rates for successive decades. The
amplitudes of these indentations become larger as one moves back in time.

**Identification of the underlying diseases**

Fig. 2b suggests that the deviations were stronger in the first half of the 20th century; however, they may still exist (albeit in reduced form) in present-day data. If this assumption is correct it will make their identification much easier because we will be able to use the “CDC WONDER” database which covers the period 1999-2014 and provides unparalleled accuracy as to the causes of death. The fact that the database covers 16 years and for a large country is important because even if the effect that we wish to detect is much smaller than in the early 20th century we may nevertheless have a chance to see it.

As one goes through various causes of death, e.g. cancer, heart diseases, malformations, metabolic diseases, enteritis, bacterial diseases, viral diseases, it becomes quickly clear that only the last two in this list show visible peaks. These are shown in Fig. 3.

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![Fig. 3 Death rates for viral and bacterial diseases, USA, 1999-2014.](image)

The ICD10 code numbers for viral infections and bacterial diseases are \((A80 – B34)\) and \((A00 – 09 + A30 – 49)\) respectively. The two peaks are found approximately at the locations where they were expected. The right-hand side of the graph shows that in contrast with bacterial diseases (as well as most other diseases) the age-specific death rate of viral infections deviates strongly from the Gompertz-like exponential growth. The reason for that deviation remains an open question. *Source: CDC WONDER database, 1999-2014.*

Can we identify them with the indentations displayed in Fig. 2b. Two reasons make this identification plausible.

- The peaks displayed for viral infections on the one hand and bacterial diseases on the other hand are roughly positioned where we expect them. However, this
reason is not completely compelling because of the lack of accuracy due to the small number of data points. Over the first year after birth the data given by WONDER are limited to the standard postnatal intervals: 1st day, 1-7d (early neonatal), 7-28d (neonatal), 28-365d (late neonatal).

- Are the amplitudes of the peaks of Fig. 3 consistent with what we expect? The steady decrease of the amplitude of the indentations seen in Fig. 2b makes us expect fairly small deviations in the period 1999-2014. This is indeed the case. For the 16 years of the period under consideration the first three data points of the curve for viral infections correspond to a total number of deaths of 30, 44 and 371 respectively, that is to say 1.8, 2.7 and 23 deaths annually. These are very small numbers. Incidentally, we see that more age intervals would lead to even smaller numbers (hence more statistical fluctuations) and therefore would not be very useful. In addition, it is clear that the contribution of these deaths to the total mortality is very small and is therefore undetectable in the curve for “all causes”.

A last comment is in order regarding the left-hand graph which covers the adult age interval 10-90. Strictly speaking, this graph is not necessary for the present investigation. However, it may be of interest because of the sharp difference in shape of the two curves. In old age, the bacterial death rate is 200 times larger than the viral death rate. No doubt, such a huge difference has a biological significance.

### Magnification of the signatures of viral/bacterial diseases

In the previous sections we were able to locate the peaks and to identify the diseases that they describe. In addition we saw that, unsurprisingly, these peaks had been markedly reduced in amplitude over the past century. Thanks to this understanding, we can now get a more accurate picture of these signatures. For that purpose we need to introduce two improvements.

- We need to view these diseases in the past when their amplitude was still larger.
- We need to find datasets which provide as many data points as possible over the age interval (0, 10).

As we already observed, these conditions go hand in hand in the sense that the second would be useless if the number of deaths is too small for then most of the age intervals would have small numbers of deaths that would give rise to large statistical fluctuations.

When one wants to go back in time one must be careful about two things.

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1 That is why we cannot give similar data for Switzerland. As its population is 37 times smaller than the US population one would not see a single death.

2 At the peak value of viral diseases, the 371 deaths represent only 0.65% of the total number of 56,616 deaths in this age interval.
There is a major difference between the data provided by the CDC WONDER database and those given in the digitized paper volumes of the “Vital Statistics of the United States” in the sense that the VSUS volumes give the death numbers for a selection of causes whereas WONDER gives them for all causes.

In addition, the list of death causes (and also their definition) has been changing with successive revisions of the “International classification of diseases”.

For our present purpose, this has two direct implications.

1. In the VSUS volumes the cause “Viral diseases” appears only in 1968; thus we cannot go back in time earlier than 1968. Moreover in the first years after being introduced this entry has fairly irregular data. That is why we considered the time interval 1973-1975.

2. The entry “Bacterial diseases” does not exist in the VSUS volumes and as the entries are only a selection it would be hazardous to set it up by combining several sub-entries. For this reason we prefer to focus on one specific bacterial disease, namely tuberculosis. As is well known, tuberculosis was the major cause of death in the United States in the early 20th century.

Viral diseases

Fig. 4 shows the peak of viral diseases. It extends from 5 to 22 days after birth with a peak value at 10 days. This peak is not only present in the US for all years for which data are available, we have also seen at the beginning that it exists as well in Switzerland. What questions do these curves raise? Just as illustrations one can mention the following points (probably medical doctors would raise many others).

1. One may wonder why there was an overall decrease over the 16 years between the two time periods. As far as we know, between 1973 and 1993 there was no vaccination before the 10th day after birth.

2. Even if one accepts the overall reduction as a fact, it can be observed that the reduction was much smaller around the peak value than elsewhere; this raises another question.

Bacterial diseases: tuberculosis

Fig. 5 shows the peak for tuberculosis considered as representative of the broader class of bacterial diseases. It is much (130 times) wider than the viral peak and extends from 25 days after birth to the age of 6 years. This peak is not only present in the US it is also present in Switzerland. Because the disease was very serious at the end of the 19th century fairly detailed data are available for 1877-1881. The corresponding curve is parallel (albeit higher as would be expected) to the US curve.

\[\text{Unfortunately the Swiss Office of Statistics does not seem to have data by age for this ICD entry. Thus, one cannot make a direct comparison. However, we are convinced that once Swiss data become available they will display a similar peak.}\]
Fig. 4  Infant death rates for viral diseases, USA, 1973-1975 and 1989-1993. The peak value occurs at the age of 10.5 days after birth. The error bars are ± standard deviation. This graph is very similar to graphs describing the yolk sac effect for fish (see for instance the graph for sturgeons in Berrut et al. 2016, graph 4a). This is not surprising because yolk is known to have an anti-body content (Kovacs-Nolan et al. 2012) which gives an immunity facet to the yolk-sac effect. Source: Vital Statistics of the United States for the corresponding years.

in 1910. The bacterial peak has also a larger amplitude than the viral peak but not in proportion to the width ratio. The peak-to-bottom ratio is 3 for the viral peak and 6 for the tuberculosis peak.

Conclusion

Spectroscopy of age-specific infant death rates

An alternative and more specific title for the present paper could have been “Spectroscopy of infant death rates”. We decided against it because it could have been confusing for some readers. However, the parallel with spectroscopy conveys fairly well the idea on which this paper relies. In spectroscopy one analyses radiation intensity as a function of wavelength in order to detect peaks which in turn will identify emission frequencies characteristic of specific atoms. Here, we analyze infant death rates as a function of age in order to characterize internal effects such as the response to exogenous factors. This paper focused on pathogens but it is also conceivable to analyze the response to a lack of food, a sudden change in temperature or a change
Fig. 5  Infant death rates for tuberculosis, USA, 1932-1936 and 1950-1952. The peak value occurs at the age of 290 days after birth. The error bars are ± standard deviation. Source: Vital Statistics of the United States for the corresponding years.

A key point was to use the death rate ratio which filters out what is common to two death rate functions and thereby reveals in what respect they are different even if this difference is a fairly small component. Here we have used this tool to compare the death rates in different time periods but such a a differential comparison could also be done for two regions or countries. Then, in the second part, we have shown how to identify the diseases responsible for the anomalies. Finally, by going back to earlier decades we could give a fairly accurate description of the viral and bacterial peaks.

As this paper is written by physicists, the question of how to interpret the shapes of the peaks given in Fig. 4 and 5 is left open. The authors limited their task to presenting the evidence as clearly as possible. Nevertheless a few explanations regarding the response of the immune system are given below.

**Transition stages of the immune system**

The broad bacterial peak is probably in relation with the transition from immunity based on maternal antibodies to an autonomous immune system. Niewiesk (2014)

4Such a study could be done by analyzing the infant death rate function of populations living over 3,500 meters. The worldwide population living permanently over 2,500 is estimated at 140 million.

5As a proof of the effectiveness of these antibodies, Moreina et al. (2007) mention the fact that babies with agam-
mentions that the inability of the immune system of the late neonate to fully respond
to an antigenic stimulus has also been observed in several other mammals, e.g. in
pigs, cows, horses, mouses, rats. That allows comparative studies in terms of age-
specific death rates. This will be our next objective.

Appendix A. Plausible model for the hyperbolic fall

With this plausible model our purpose is to show that it is not difficult to imagine a
mechanism which produces an hyperbolic fall of the death rate. We call it a “plaus-
bile” model because it just one possibility among an indefinite number of possible models.6 This model as well as the previous ones are unsatisfactory in the sense that they do not allow any testable prediction; this is because the parameters which they
include cannot be measured independently.

The mechanism of the model is explained in Fig. A1.

![Fig. A1](image-url) A mechanism which leads to an hyperbolic fall of the death rate. It is because the x-scale is logarithmic that the fraction $p$ is represented by intervals of same lengths.

We suppose that there is a spread in a physiological variable. In Fig. A1 we consid-
ered heart rate. It is natural to assume that those individuals for whom the variable is
farthest away from the reference value will die on the first day (we denote them by $D_1$) that those for whom the variable deviates less will die later, say on the second
day ($D_2$) and so on. It is also fairly natural to assume that the $D_i$ are a given fraction
of the the population $L_i$ alive at the beginning of that day: $D_i = L_i p$. Thus, the suc-

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6Three other models which also lead to an hyperbolic fall are described in the arXiv version of Berrut et al. (2016).
cessive values of $D_i$ become a geometric progression. As a result, the infant death rate, defined as the number of deaths divided by the number of live births, will also be a geometric progression: $\mu_b(t) \sim (1 - p)^t$.

Note that to make the model testable one should be able to estimate $p$ independently.

Appendix B. Experimentation in physics versus biology

Experimentation in biodemography

Our approach is to start from patterns and regularities observed in humans and then to see whether (and to what extent) they are shared by other species. Human demography belongs to the social sciences in the sense that one cannot do experiments. In contrast in the field usually referred to as “biodemography”, it is possible to do experiments. One would therefore expect experimentation in biodemography to be fairly close in its essence and objectives to experimentation in physics. That is not so however and in this Appendix we try to understand the reasons and implications.

At what level should one observe complex systems?

Nowadays biologists have at their disposal highly sophisticated techniques of investigation which give them access to detailed mechanisms at the level of proteins and other macromolecules. While such techniques represent a great opportunity, there is also a possible downside in the sense that to have too many details may hinder global understanding. When a description of apoptosis (i.e. programmed cell death) involves dozens of physical processes (e.g. folding, unfolding, sticking, diffusing) and chemical reactions it becomes difficult for a human mind to make sense of it. To say it differently, if in their exploration of matter physicists of the eighteenth and nineteenth century have had at their disposal Raman spectroscopy, slow neutron scattering and X-ray diffraction they may have refrained from proposing some of the crude, yet nonetheless very useful, phenomenological laws on which the physics of that time relied. It was a piece of good luck that in the development of physics progress in our understanding and means of observation progressed in sink.

The key of comparative analysis

However, if the availability of precise means of observation at the molecular level is one part of the explanation, it cannot in itself explain why cross-species comparative studies have become very rare. In physics, the comparative perspective was essential from the very beginning. Once a new physical effect had been identified the main goal was always to determine its scope of occurrence. For instance, gravitation coupled with Newton’s law describes the fall of apples, but also the phenomenon of the tides, the movement of the Moon around the Earth and (at least to some extent) the
rotation of galaxies around their center.

When we started our investigation of infant mortality we were surprised to see that despite of the very remarkable law governing human infant mortality, there had been no studies which addressed the question of whether other species followed the same law. Thus, our first investigation (Berrut et al. 2016) was to answer this question. We found the same pattern in mammals and fish. In our paper we used our own data for primates and for other species we relied on existing data. However, all such data had been collected for reasons which had nothing to do with the purpose that we had in mind. They were recorded mostly for economic reasons because for farmers it is obviously of interest to know postnatal mortality of farm animals. The same observation applies to fish with respect to aquafarming. Whether beyond mammals and fish the same pattern also extends to “simpler” organisms (e.g. C. elegans) is at the present moment still an open question; it is under investigation in a series of experiments.

**Why is there a reproducibility crisis in biology and soft matter physics?**

Apart from the lack of comparative perspective, another important feature of biological experiments is the fact that they are rarely repeated. A recently published editorial in the journal “Nature” (Vol. 533, 437, 26 May 2016) mentions that two-thirds of the researchers who responded to a survey think that the current lack of reproducibility is a major problem. To the mostly circumstantial reasons that are given in the editorial one can add a more fundamental factor which is precisely the lack of comparative perspective already mentioned. Indeed, if a mechanism has a broad range of validity it makes sense to measure it with utmost accuracy. In physics, whenever a measurement is “repeated” this is almost always done for improving its accuracy. Actually, even in physics an experiment is never strictly “repeated”; it is done under conditions in which one expects indeed the same effect to be observed but these conditions are never exactly the same as in the observations conducted by other teams. While improving the accuracy is a major incentive for “repeating” an experiment, when this incentive does not exist it is quite understandable that few experiments are repeated.

**Medicine-oriented funding**

In the physical sciences there is a clear separation between fundamental physics and engineering. The funding of fundamental physics is largely independent of any perspective of practical applications. As an illustration one can mention the funding of the “Large Hadron Collider” whose main success so far has been the discovery of...
of the Higgs boson, a particle which has a lifetime of only $10^{-22}$ s. In the same line of thought one can mention the funding of the expensive telescopes which are necessary in astrophysics.

On the contrary, in biology there is no clear separation between fundamental biology and medicine in the sense that funding is much influenced by the war against various diseases, e.g. cancer, Alzheimer’s disease or other degenerative diseases. Even for research of a fairly fundamental nature, discovering new treatments is a permanent temptation for researchers because of the fame and social rewards attached to such discoveries.

References

Berrut (S.), Pouillard (V.), Richmond (P.), Roehner (B.M.) 2016: Deciphering infant mortality. Physica A 463, 400-426.

CDC WONDER is a mortality database set up and maintained by the “Centers for Disease Control”. It is available at the following address: [http://wonder.cdc.gov/ucd-icd10.html](http://wonder.cdc.gov/ucd-icd10.html).

Encyclopédie statistique de la Suisse. Statistique historique. Section: Santé. Sous-section: Mortalité et causes de décès [Statistical Encyclopedia of Switzerland. Historical Statistics. Section: Health. Subsection: Mortality by causes of death.] Available on Internet at the following address: [http://www.bfs.admin.ch/bfs/portal/fr/index/infothek/lexikon/lex/2.html](http://www.bfs.admin.ch/bfs/portal/fr/index/infothek/lexikon/lex/2.html).

Kovacks-Nolan (J.), Mine (Y.) 2012: Egg yolk antibodies for passive immunity. Annual Review of Food Science and Technology, 3,163-182.

Linder (F.E.), Grove (R.D.) 1947: Vital statistics rates in the United States 1900-1940. US Government Printing Office, Washington DC.

Moreina (B.), Blomqvist (G.), Hu (K.) 2007: Immune responsiveness in the neonatal period. Journal of Comparative Pathology 137,S27

Niewiesk (S.) 2014: Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Frontiers in Immunology 5,446.