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Congenital anomalies from a physics perspective. The key role of "manufacturing" volatility

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ABSTRACT

Genetic and environmental factors are traditionally seen as the sole causes of congenital anomalies. In this paper we introduce a third possible cause, namely random "manufacturing" discrepancies with respect to "design" values. A clear way to demonstrate the existence of this component is to "turn off" the two others and to see whether or not there is still remaining variability. Perfect clones raised under well controlled laboratory conditions fulfill the conditions for such a test. Carried out for four different species, the test reveals a variability remainder of the order of 15% in terms of coefficient of variation (i.e. ratio of standard deviation to average, subsequently denoted by CV). As an example, the CV of the volume of E. coli (Escherichia Coli) bacteria immediately after binary fission is of that order.

In short, "manufacturing" discrepancies occur randomly, even when no harmful mutation or environmental factors are involved. If the pathway is particularly long or requires exceptional accuracy, output dispersion will be high and may lead to malformations. This effect will be referred to as the *random dispersion effect*. We conjecture that it will be particularly significant when major changes occur; this includes the early phase of embryogenesis or the first steps leading from stem cells to differentiated (organ-specific) cells.

The dispersion effect not only causes malformations but also innocuous variability. For instance monozygotic (MZ) twins resemble each other but are not strictly identical. It is not uncommon to see only one of the twins of a MZ pair showing a congenital defect (see Appendix A).

Not surprisingly, there is a strong connection between congenital defects and infant mortality. In the wake of birth there is a gradual elimination of defective units and this screening accounts for the decline of postnatal infant mortality. In humans, for reasons which are not yet understood, this decline continues until the age of about 10 years. Neither do we understand why, as a function of age, the downward trend of human infant mortality follows a power law with an exponent around 1 (whereas for fish it is

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about 3, see Bois et al. 2019a). Apart from this trend, post-natal death rates also have humps and peaks associated with various inabilities and defects.

In short, infant mortality rates convert the case-by-case and mostly qualitative problem of congenital malformations into a global quantitative effect which, so to say, summarizes what goes wrong in the embryonic phase.

Based on the natural assumption that for simple organisms (e.g. rotifers) the manufacturing processes are shorter than for more complex organisms (e.g. mammals), fewer congenital anomalies are expected and therefore also lower infant mortality. How this conjecture can be tested is outlined in our conclusion.

This paper is the first leg of an exploration in three parts; parts 2 and 3 are Bois et al. (2019a,b). Despite their connections, the three papers can be read independently from each other.

1. Introduction: the "manufacturing dispersion" effect

Genetic and environmental factors are usually seen as the only sources of birth defects. Even when multifactorial effects are considered they are interpreted as a combination of genetic and environmental causes.[1] Here, we add a third source referred to as a "manufacturing dispersion" effect. Its introduction is motivated by several reasons which are outlined in coming subsections. However, the basic idea that we develop is quite simple and will certainly seem natural to all physicists. It is the recognition that in any ensemble of items produced in a manufacturing process involving many steps, there will be a small percentage which are defective. For instance, in the production of high quality violins some will have a first rate sound while others will have a second or third rate sound. This is not due to any specific reason but to the random dispersion which exists in any statistical ensemble.

1.1. Variability in biochemical reactions triggers volatility in cell characteristics

Hundreds of biochemical reactions are required for the growth of any living organism even if it is a single cell. Taken together they constitute what one may call a manufacturing process. For each of these reactions there is a set of optimal parameters in terms of temperature, pH, concentration of enzyme-catalyst, orientation and shape of interacting molecules and so on. It is clear that mutations and environmental factors may disrupt this process. However, in the present paper we develop the idea that even if all parameters are set at their optimal "design" values[2] nevertheless there will be a dispersion of the outcomes. It has four main causes. (i) Initial conditions may not be identical. (ii) Even if initial conditions are very similar, there will be "butterfly effects" (due to the nonlinearity of the reactions) which will greatly amplify any initial dissimilarities no matter how tiny. (iii) The parameters defining the reactions are never *exactly* at their optimum values. (iv) Random quantum fluctuations cannot be avoided. Note that this last effect is probably smaller than the others.

Even if at each step the variability is small, a succession of steps will result in a cumulative effect which, eventually, may lead to noticeable congenital anomalies.

As an illustration of this kind of variability consider an observation made at the level of individual cells. According to a recent study [2, p. 729, 733, Fig. 4B,C], isogenic *E. coli* cells (i.e. having same genotype) growing in a uniform and invariable environment display significant variability in volume at birth (i.e. volume immediately after binary fission) and in individual growth rates. The coefficients of variation are fairly substantial, of the order of CV $\simeq$ 10%, 20% respectively. Incidentally, as will be documented later on, variability at cell level has already been recognized and studied (at least qualitatively) in the 1910s and 1920s.

1.2. From technical systems to living organisms: a physics perspective

In this paper we examine biological systems from the perspective of reliability engineering. Such a comparative approach is rather uncommon in biology; in contrast, comparative analysis plays a key-role in experimental physics. Therefore, it is perhaps not surprising that this approach is tried by physicists and biologists who share a similar turn of mind.[3]

[1] E.g. one can cite the following sentences from the website of "Boston's Children Hospital": "Most birth defects are caused by genetic or environmental factors or a combination of the two. In most cases, however, the cause is unknown. Multifactorial birth defects are caused by a combination of genes and environmental exposures. In other words, a person can inherit a gene that increases sensitivity to an environmental trigger". In the same spirit, one can mention the first sentences of the abstract of Chen et al. [1].

[2] In practice this means: (i) a time interval sufficiently short to ensure that the likelihood of mutations is negligible compared to other reactions. (ii) constant optimal environmental conditions of the kind maintained in controlled laboratory experiments.

[3] Not long ago, in an email of 31 December 2018, Prof. Bert Vogelstein, a biologist renowned for his work on cancer, told us: "We need more physicists thinking about cancer". Such a statement was certainly an encouragement to go in this direction.

Why should it be useful to establish a link between technical and living systems? In physics it is natural to take systems that we understand fairly well as starting points for the investigation of phenomena that remain mysterious.[4]

One should not focus only on similarities, differences may also be revealing. A rather obvious illustration is that, whereas in engineering the duplication of critical components is a common technique for improving reliability, mammals have only one heart, not to speak of many other vital organs for which there is no backup. For instance, urinary retention can occur for many reasons whether physiological or neurological and, if not remedied, may lead to death within a few hours. Yet, there is no backup mechanism. We are told that Tycho Brahe, one of the founding fathers of modern astronomy, died that way. This example is of interest because, whereas adding a second heart would require a considerable design change, creating a supplementary bladder outlet would be a fairly simple matter.

1.3. Broad reach of congenital anomalies

Malformations versus deficiencies. This paper is mainly about congenital anomalies. We prefer this expression to birth defects for two reasons: (i) Many anomalies do not appear in the form of malformations but as deficiencies, e.g. insufficient production of insulin in Type 1 diabetes. (ii) Many congenital anomalies do not appear at birth nor even in childhood but much later in the course of life; anomalous heart valves are an example that will be discussed later on. Behavioral anomalies may also appear only later in the course of life. Having said that, we will sometimes also use "birth defects" which has the advantage of being shorter.

Anomalies of the immune system. It should be noted that in fact it is difficult to separate mortality due to congenital anomalies from other causes of death. Even cancer or mortality from infectious diseases may be attributed to congenital anomalies of the immune system. In this respect one should remember that even in major epidemics such as the Spanish influenza pandemic of October–November 1918, less than 10% of the population was affected in the sense of being hospitalized and only about 0.4% died, which means that most persons were protected by their immune system. Only a few were not.

Behavioral anomalies. We give much attention to this case. Why? As for phenotype, the behavior of organisms results from the interaction between heredity and external factors; this is the so-called dialog between innate and acquired, between nature and nurture. However for the biochemical reactions which lead to somatic defects we can hardly know what are the optimum values of temperature, pH and other parameters, neither do we know the real conditions prevailing in the embryo in a given stage. On the contrary, one can know the ideal parameters which lead to the hatching of eggs; for instance, through experiments one can determine how many times per day eggs need to be turned up side down. This value can then be compared to the actual frequency observed in the brooding process (see below). In other words, provided it is done in a rigorous way, a detailed behavior analysis gives a rare opportunity to observe and better understand the interplay of heredity, environment and random fluctuations.

As an illustration we consider the case of a broody hen. From the eggs laid by the hen to the hatching of chicks 21 days later, there is a succession of steps which is quite remarkable. For most of these steps it is possible to know the optimum conditions. The description given below has two useful implications.

- It shows on a real case how successive steps are linked. Biochemical reactions also occur in steps but their succession is more difficult to analyze.
- The analysis of successive steps confirms a basic rule, namely that inappropriate conditions are more harmful in the first steps than in the last, a point that is also made in Uchida et al. [3].

(i) *Fertilization.* The process starts when the eggs are fertilized by the rooster inside the hen's body. (ii) *Physiological changes.* The beginning of the process is also marked by physiological changes: the body temperature of the hen increases and the feathers under her body fall off. (iii) *Making a nest.* The hen makes a nest about 5 cm deep by scratching the ground. If the nest is too shallow the eggs will tend to roll outside which will derail the whole subsequent process. (iv) *Storage of the eggs.* As the hen will brood a set of about 6 to 10 eggs, over several days she will lay eggs and store them in the nest. As soon as an egg has been laid, it will cool down and the content will contract whereby the air cell is created. It will play a crucial role during hatching because it is always on this side that the chicks will pierce the shell. (v) *Sitting on the eggs.* While sitting on the eggs, the hen will have to turn them in order to prevent the embryonic chicks from sticking to the shell. As well as turning them, she will also move the eggs located on the periphery of the nest into the middle and the middle ones out so all are evenly warmed. A graph (Fig. 3d) presented in the section on embryogenesis shows that there are very strict temperature requirements. (vi) *Cleaning the nest.* The hen will have to keep the nest clean and tidy which, in particular, means that non-fertilized or broken eggs must be discarded. (vii) *Taking breaks.* The hen will leave the eggs a few times a day (each time for about 15 min) to find food and water and to defecate. (viii) *Last three days.* During the last three days the embryos start to produce significant levels of metabolic heat. Therefore, brooding should be relaxed. When the chicks start to break their shells the hen must give them enough room. (ix) After hatching the chicks remain mostly underneath the hen thereby sharing her body heat. For the same reason, after hatching in an incubator chicks are kept warm by infrared lamps. They are fully feathered only at six weeks of age.

[4] Many such cases can be found throughout the history of physics. One of the most recent examples is how electromagnetism, more precisely quantum electrodynamics (QED) was used as a guide for building a theory of strong interactions, namely quantum chromodynamics (QCD).

This process was described in detail to show how easily it can be disrupted or become sub-optimal (in the sense of a reduced hatching rate). Whereas for many malformations the adverse factors remain hidden to outside observers, here, on the contrary, inappropriate environmental conditions occur in full view and can be identified. To our knowledge, this field of research has not yet been explored in a systematic way.

Just as for phenotype variability, there is also a volatility in brooding ability. Some hens are good brooding hens while others are not.[5] In the same way as most birth defects are nothing but extreme forms of normal variability,[6] similarly some forms of behavior are sufficiently extreme to be labeled as "abnormal". Here are two examples.

- First time brooders might not remain on their nests for very long which, of course, leads to the failure of the whole brooding process.
- On the contrary, some hens may sit on *empty* nests for 2 or 3 months.

1.4. Randomness of the dispersion effect

The main defining characteristic of the dispersion effect is its randomness. However, this word does not mean that anything can happen and that nothing can be predicted. In fact, there are predictable consequences.

- For instance the dispersion does not manifest itself in the same way in a process that requires high accuracy[7] than in one which does not. Several illustrative examples are described below.
- Whether the dispersion occurs at the beginning or at the end of a pathway[8] will also make a difference.

1.5. Rationale for an output dispersion effect

There are several motivations for introducing the dispersion effect.

(1) **Most birth defects are unexplained.** For most birth defects the factor responsible is not known. A recent publication in the "British Medical Journal" [4] tells us that in a total of 5504 birth defects in 270,878 children born in the state of Utah in 2005–2009, the etiology is unknown for 3390 which represents 80% of the cases. Of the 1104 cases for which the etiology is known, 844 are due to chromosomal abnormalities which are mostly trisomy 13, 18 and 21. In our conception most defects occur randomly, so it is hardly surprising that many remain unexplained.

(2) **Variability in true twins.** Many articles give the (misguided) impression that most malformations can be attributed to specific genes. If this were true, the twins of monozygotic pairs would have the same birth anomalies. In fact, as shown in Appendix, the discordant cases (where the two twins do not have the same defect) are 4 times more frequent than the concordant cases (where they share the same defect).

At this point it is necessary to say a word about epigenetic changes, a notion which refers to how genes are expressed rather than to their identity. The present-day consensus is that to be considered epigenetic a trait has to be heritable at least for a number of generations. This is certainly a wise rule for otherwise any difference occurring between true twins could (somewhat arbitrarily) be attributed to epigenetic factors.

(3) **Variability of offspring in uniparental reproduction.** Inheritance from two parents is a difficult problem. The study of true twins is one way to overcome this difficulty. The study of reproduction from a single parent is another. Uniparental reproduction was much studied between 1900 and 1930 particularly at the "Zoological Laboratory" of John Hopkins University; see the studies of Stocking [5,6], Middleton [7], Jennings [8] and Noyes [9]. Uniparental reproduction (also called asexual reproduction) occurs in two cases.

The simplest is the reproduction by fission of unicellular organisms. In her thesis [9] Bessie Noyes cites four species of protozoans for which inheritability was studied.

The same kind of investigation can be made for multicellular organisms (i.e. metazoans) with uniparental reproduction. For instance, in rotifer species during its life time of a few days one female can generate successively of the order of 10 offspring. Although they are in a sense clones of their mother, they present a substantial variability [9].

It is true that one can never exclude that a somatic mutation (i.e. a DNA alteration) occurred during the embryogenesis of offsprings. Yet, it is well known that errors in protein synthesis are far more frequent than errors in DNA replication [10].

(4) **Dispersion of outputs.** The three previous points explain that there is room for a third source of birth defects but it does not describe what this source could be. It results from the fact that in any manufacturing process[9] there are two stages: (i) The design phase (ii) The implementation of the design. For living organisms it is the DNA–RNA code which represents the design instructions destined to the manufacturing process.

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5 A simple test consists in putting an egg in front of a hen. If she pulls the egg under her she may be well "gifted".

6 For instance, between thumb atrophy and a thumb that is normal there is a range of intermediate cases involving small, underdeveloped thumbs.

7 For instance, for the eyes even a small dissymmetry may result in strabismus. For the ears synchronization requirements are less critical.

8 In molecular biology the term "pathway" has a technical meaning in reference with the expression of genes. Here, we use the word more broadly as referring to a succession of steps realizing a given function. It can be a cascade of chemical reactions or also a succession of actions. An illustration is the feeding function which requires an organism to see the prey, then to identify and catch it and finally to eat and digest it.

9 To use for living organisms the expression "manufacturing process" may seem odd. However, our objective is precisely to study living systems from the perspective of technical reliability science.

In real life, a design is never carried out with absolute accuracy. If a table is designed with a width of 3 m, in reality its width will be comprised between $W_1 = 2999$ mm and $W_2 = 3001$ mm. For most practical usages such small discrepancies are of no consequence. However, if one wants to bring the table into a room whose door has a width of 3 m, then the W_1 table will fit through whereas the W_2 table will not.

This is a static view. As soon as there is a nonlinear process evolving in time (which is the case of most biochemical reactions) there will be butterfly effects through which small initial differences are amplified.

(5) **Crucial role of early discrepancies** In 2015 it was shown that mutations which eventually lead to cancer cells may occur at different stages of the transformation of undifferentiated stem cells into mature differentiated cells [11]. This discovery provided a natural explanation for the fact, known since the 1920s [12,13], that cancer cells which have a low degree of differentiation are also the most malignant, that is to say, result in early recurrence and death. Indeed, a mutation occurring early in the differentiation process will impact and derail all following stages.

There is a similar feature with the embryo itself in the sense that it is in the earliest stage of their development that organs are the most sensitive to teratogenic (i.e. causing developmental malformations) factors. This point is shown very clearly in a paper by Uchida et al. [3]. In this study various shocks (e.g. heat shocks) were applied in different stages of the embryo development of zebrafish, frogs and chicken. In all cases embryonic lethality was the most severe when the shock was applied in the earliest stage.

This observation has a natural interpretation in the manufacturing framework; it says that a small defect in a component *A* used in the early stages of a production chain may have quite detrimental consequences because it may hinder the appropriate working of components introduced later on in the process and with which *A* is functionally related.

The manufacturing conception developed in this paper is consistent with (yet broader than) the mechanism identified in Tomasetti and Vogelstein [11] and which the authors describe as follows:

> "The concept underlying the current work is that many genomic changes occur simply by chance during DNA replication rather than as a result of carcinogenic factors". Therefore, one expects a correlation between "the lifetime number of divisions among the stem cells within each organ and the lifetime risk of cancer arising in that organ".

Each division bringing about a further step in the differentiation process also represents a new manufacturing challenge which makes it more prone to output dispersion than mere divisions into identical daughter cells. Whether the discrepancy occurs by mutation or by output dispersion, its impact will be more severe if it occurs early in the differentiation chain.

In medical language, such early cell anomalies are labeled as pre-cancerous conditions. They are characterized by the presence of abnormal cells, yet in low proportion and in shapes which are not very different from normal types.

In the manufacturing of living organisms mechanical operations play a role (see Table 1) but most pathways consist of a succession of chemical reactions. The previous argument remains valid however. Conditions of concentrations, temperature, acidity or other parameters are never 100% optimum; as a result, the outputs will have a dispersion around optimal design values.

(6) **Critical processes are the most affected.** Under the term "critical processes" we understand processes which require high synchronicity and accuracy. Whenever two sheets must grow at the same speed in order to join seamlessly, even a slight discrepancy may affect the closure. Examples of defects of this kind are:

- Spina bifida, a defect of closure around the spine. From the open to the closed form there is a broad range of severity for this defect. "Spina bifida occulta" is a closed form which is quite frequent; it affects 15% of newborn according to estimates but causes no symptoms. About this case one can read the following assessment: "The exact causes of spina bifida occulta are not well understood. Both genetic and environmental factors seem to play a role". Our thesis is that there are *no* causes; it is a purely random effect. The fact that slight defects are much more common than severe defects is consistent with a dispersion mechanism. An explanation based on mutations is less satisfactory. It is true that severe forms may affect the reproductibility rate and therefore the transmission of possible genetic factors but there would be little difference in this respect between light forms and very light forms.
- Cleft lip and palate or more generally facial cleft.
- The positioning of the eyes (i.e. iris+pupil+lens) also requires high accuracy because the two eyes must move in a synchronized way. For each eye positioning relies on two muscles (one on each side) whose actions must be perfectly coordinated. As it is not easy to achieve such high accuracy requirements it is hardly surprising that, as shown in Table 1 strabismus is one of the most frequent birth defects (2% of births).
- Heart valve defects are almost as frequent as strabismus. More details will be given later.

1.6. Control procedures

In industrial production there are control procedures all along the supply and production chains. There are certainly similar control procedures in the making of living organisms. Although we do not know them very well there has been progress in this direction in recent decades. For instance, the role played by the non-coding region of the genome (which represents 98.5%) is becoming clearer.

Spontaneous abortion can be seen as a control mechanism but the occurrence of live births with severe malformations (e.g. anencephaly, that is to say newborns without a brain, whose prevalence is about 120 per million births) shows that

Table 1
Incidence of birth defects in high accuracy processes.
Source: Child health, USA 2014, Table 1: National prevalence estimates of selected major birth defects; Gunton et al. [14]; for spina bifida occulta: estimate of the "National Institute of Neurological Disorders and Stroke".

Birth defect	Description	Prevalence (per 1000)
"All" birth defects		30
Cases with "geometrical" defects		
Strabismus	Eyes not properly synchronized	20
Heart valves defects	Abnormal joints of cuspids	10
Cleft palate and/or cleft lip	Facial sheets do not join well	1
Spina bifida (open)	Defect in spine closure	0.4
Spina bifida occulta	Slight defect in spine closure	150
Among children with trisomy 21		
Strabismus	Eyes not properly synchronized	350
Heart	Serious congenital heart defects	400

Notes: Prevalence is defined as the total number of births affected by the problem in a time interval of several years compared to the total number of live births in the same time interval. All these cases are characterized by "mechanical" or "geometrical" defects. The cuspids designate the leaflets which form the heart valve. In most valves there should be three leaflets; when two leaflets stick together it is a bicuspid defect. There can also be 1 or 4 cuspids but these defects are fairly rare. Incidentally, the fact that the prevalence of the four causes mentioned is higher than the "all defect" prevalence estimate shows that the "all defect" notion does not include some light cases (e.g. light strabismus or spina bifida occulta) or defects which manifest themselves only later in the course of life (e.g. light valve defects). Most often spina bifida occulta (i.e. not visible) causes no symptoms and is only identified through X-ray imaging.
Trisomy 21 (that is to say three chromosomes number 21 instead of two) results in over-production of the proteins under the control of the 310 genes located on this chromosome. This disrupts many mechanisms and particularly those requiring high accuracy: brain (100% are more or less affected), heart (40% serious congenital anomalies), eyes (strabismus affects 35%), ears (hearing loss affects 70%).

this control is insufficient. It is true that apoptosis (that is to say programmed cell death) is a local control mechanism, but it is surprising that massive defects at macro level are not identified and corrected. In our industrial analogy it would mean producing aircraft without wings.[10]

The dispersion conception would also suggest more frequent defects in highly complex organs than in simpler ones. However, before we discuss this point we need to assess the reliability of defect statistics.

1.7. Why defect statistics give a biased picture

The statistics of birth defects released by hospitals give a picture which is biased in (at least) three respects.

(1) Very serious defects usually will lead to early abortion or still births. This fact can be illustrated by the following data. In 13,614 births that occurred in an hospital of Rajasthan (India) in 2012 there were 431 stillborn and 13,183 live-births. Among the stillborn, 18% had a birth defect whereas only 0.64% of the live-births had a defect [15]. Thus, many serious cases will not be included if birth statistics are restricted to live-births.

(2) Many slight defects will not be recorded because they will give rise to symptoms only much later. This can be the case even for heart defects; for instance light valve defects or stenosis (i.e. narrowing) will be noticed only at the age of 40 or 50. It is the same problem for many other internal defects. Whereas polydactyly (i.e. more than 5 fingers) can be detected visually just by inspection, many slight defects of internal organs may never appear or appear only later in life.

(3) For a complex organ like the brain, there is no well defined border line between what is normal and what is not. Thus, the fact that some persons can sing very well while others cannot will not be considered as a congenital defect. Even more serious defects (such as a propensity to autism) will appear only later on in life; as a result the respective role of genetic, environmental or dispersion factors will remain unclear. For that reason, although the brain is by far the most complex organ of a human body, it will be left aside in the next subsection where we discuss the role of complexity.

1.8. Are complex organs more affected by output dispersion?

The manufacturing process of an airliner requires more accuracy and controls than the production of bicycles. Similarly, in a human body some organs are more complex than others. Obviously, the heart is a more complicated device than the bones,[11] the skin or even the liver. Therefore, the fact that heart defects are the most frequent congenital malformation comes as a nice confirmation of the dispersion conception.

[10] It can be argued that this is an anthropocentric view for indeed the ability to fly may not be the main purpose. After all there are insects and birds which have wings but cannot fly.

[11] It is true that "complicated" has no obvious meaning. Even a single cell is very "complicated". In addition it can be argued that the bone marrow is very essential. What we mean here is that seen from outside a pump (which is what the heart is) is more difficult to design and build than a table leg.

In contrast, defects based on mutations are not expected to follow the same rule. It seems natural to admit that the number of mutations (including harmful mutations) is proportional to the number of genes involved in the manufacturing of each specific organ. As each gene codes for a specific protein one would have to admit that the number of proteins is in relation with the complexity of an organ. If data are available such numbers could provide a useful metric for estimating the complexity of various organs.

1.9. The most frequent defects have close links with normality

Defects, particularly minor defects, are usually "in line" with normal organs. In order to explain what we mean by this expression let us consider polydactyly defects. Can the 6th finger appear anywhere?

Firstly, one can observe that the additional finger is never perpendicular to the hand. Can it appear anywhere in the plane of the hand? Observation shows that it is much more likely to appear on each side of the hand (that is to say next to the thumb or little finger) than next to the three inner fingers. In other words the 6th finger is more likely to appear as an addition to the normal blue print rather than as a drastic change in the normal design.

A similar observation can be made for the heart valves. Consider for instance the aortic valve which is located at the beginning of the aortic artery. Whereas normally it has three leaflets the defect which is by far the most frequent is when two of them stick together. The prevalence of this so-called bicuspid aortic valve (BAV) defect is between 1% and 2%. In contrast, the quadricuspid aortic valve (QAV) is a rare congenital anomaly with an incidence of only 0.01% [16].

Why is the first defect more in line with the normal valve than is the quadricuspid? The BAV originates from the fusion of two existing leaflets whereas the QAV requires the creation of an additional leaflet with corresponding changes to the three others in order to make room for the new one. Such a defect would require significant design changes.

1.10. Weak role of genetic factors in birth defects

At first sight it may seem that the dispersion effect is only of marginal importance compared to the genetic and environmental factors. For a better assessment we use a methodology based on the observation of pairs of twins.

How similar are monozygotic twins? The fact that they may look "alike" is not sufficient proof of their similarity. This can be illustrated by a case reported in Williamson [17, p. 166]. In a study of family characteristics of congenital malformations carried out in Southampton (UK) the author reports the case of twins who were "similar in hair color, eye color, head shape, finger nail shape, teeth pattern and many other features" but one of these twins was a hydrocephalic (too high pressure of fluid in the brain) male while the other was a normal male.

It is true that no valid conclusion can be drawn from a single case but this kind of observation is confirmed by a recent study of 6752 monozygotic (MZ) twins and 13,310 dizygotic (DZ) twins in California, observed from 1957 to 1982 [18].

MZ twins share 100% of their genome whereas DZ twins share on average 50% of their genome [18, p. 18]. In Appendix we explain a method for assessing the role of genetic factors. When applied to the data given in Yu et al. [18] it leads (see Appendix) to the conclusion that genetic factors play in fact a fairly weak role in major congenital malformations. This leaves free space for (i) environmental factors and (ii) for the dispersion effect described above.

Is it possible to discriminate between (i) and (ii)? For birth defects the only environmental factors which can play a role are those which affect the mother. Many factors of that kind were considered by researchers, e.g. age, level of education, birthweight, birth order, season of birth, smoking of the mother. It appears that only smoking of the mother[12] is significantly associated with congenital defects [18]. However, why should smoking of the mother affect one twin and not the other?

1.11. Identification of output dispersion through phenotype variations

Observation of uniparental reproduction offers a fairly direct view of the effect of output dispersion. It allows the notion of "pure line" (also called "inbred line" or "inbred strain") to be defined in a rigorous way as being formed by the offspring of a single individual. In contrast, for sexual reproduction a strain is considered inbred when it has undergone at least 20 successive endogenous matings (brother–sister or parents–offspring) but even at this point the individuals are only nearly clones. That is why in the first half of the 20th century there have been many investigations of uniparental reproduction.

Fig. 1 gives two illustrations. They are followed by a table which lists causes of congenital anomalies.

The main difference between the two experiments shown in Fig. 1 lies in the number of successive generations that can be observed. For Johannsen's beans there was only one harvest per year whereas under good conditions the protozoans reproduced at intervals of 3 to 5 days, that is to say almost one hundred times faster than the beans. Another difference is that the second experiment relied mainly on results expressed in integers: either the number of spines whose range is 0–7 or the number of teeth around the mouth[13] which is an integer smaller than 17.

[12] In order to measure more accurately the influence of this factor it would be useful to do a comparative analysis covering a sample of countries with highly different levels of tobacco consumption.

[13] The mouth cannot be seen on the picture describing the fission process because it is located at the separation between the mother and daughter cells.

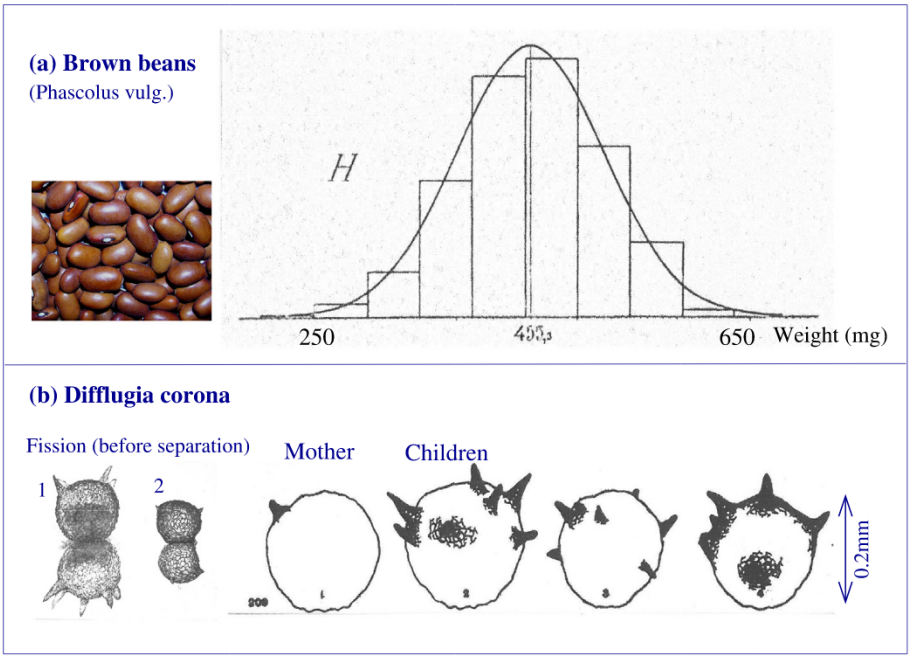

Fig. 1. Two examples of output dispersion in uniparental reproduction. Top: Dispersion in the weight of 418 bean seeds in a pure line obtained from a single grandmother seed through self pollination. The histogram is well described by a Gaussian distribution of mean $m = 455$ mg and standard deviation $\sigma = 70$ mg which gives a coefficient of variation CV = 15.4%. For all nineteen pure lines totaling 5494 beans CV = 19.9%. These experiments were done by Wilhelm Johannsen in 1900–1902. **Bottom:** Dispersion in the aspect of *Difflugia corona*, an unicellular protozoan living in water. As reproduction is by fission (as shown on the left-hand side for two pairs differing in size) all 3 descendants of the first individual (at the left) are clones. However, there are variations in their aspect at time of fission, particularly in number of spines on the shell. Note that natural self-pollination is not exactly the same thing as asexual uniparental reproduction; the later produces real clones whereas in the former (when performed naturally) there is a high degree of inbreeding which however may be somewhat less than 100%.
Source: Johannsen [19, p. 22–28] and Jennings [8, p. 438–439]

Table 2
Mechanisms related to congenital anomalies.

Mechanism	Passed to offspring Yes/No	Identification test	Example
Design glitch			
Mutation in DNA of gem cells	Yes	Genome sequencing	Trisomy 21
Mutation in DNA of somatic cells	No	Non inheritable abnormal cells	Cancer
Manufacturing glitch			
Environmental interference	No	Epidemiological studies	Effect of nicotine
Random output dispersion	No	Uniparental reproduction	Strabismus
Repair mechanism			
Apoptosis (programmed cell death)	No		Finger separation in embryo

Notes: Four comments are in order.
• It is the word "random" which characterizes the difference between items 3 and 4. It means that dispersion in outputs occurs even in optimum conditions, i.e. when no harmful environmental factor is present.
• Mutation and repair mechanisms can hardly be separated for most often we can see only their combined effects. If the cells resulting from a somatic mutation are quickly eliminated through apoptosis nothing will appear.
• Uniparental inheritance tests allow a distinction between (2) and (3)+(4). If, as seems natural, the amount of somatic mutations increases with time, their contribution to *congenital* anomalies should be fairly small. Moreover, when (3) can be excluded in the controlled environment of a laboratory experiments, then (4) seems the most likely mechanism for the abnormalities shown in the text.
• Epigenetic mutation was not included in the table for its status does not seem clearly defined. For instance, one of its mechanisms involves the addition of methyl radicals CH_3 to the molecules composing the DNA but what triggers this addition remains unclear.

A study with a similar objective was published in 1915 by Ms. Ruth Stocking which was based on variations occurring in paramecia (*Paramecium caudatum*), a large unicellular organism which lives in fresh water. Here again, as reproduction is by fission (and does not involve conjugation episodes), the descendants of each single individual will constitute a pure line. The study focused on the shape of the paramecia. A recapitulation figure (p. 408) shows a bewildering diversity of forms from the standard ellipse to strange shapes with many tentacles.

How can one account for the variations observed in those experiments? Standard factors are listed in Table 2. Item 1 is clearly excluded because the changes were not inheritable. Item 2 seems unlikely. If somatic mutations are random and independent from one another their number *must* be proportional to the number of cells[14] and to the time interval. Thus, for unicellular organisms observed at fission time this effect should be minimal.

What can be said about item 3? With a little imagination one can easily suggest possible environmental factors. Thus, for beans one can mention the position of the beans in the pods or the location of the pods on the plant. However, such "explanations" are fairly arbitrary in the sense that such factors have never been shown to lead to the almost perfect Gaussian distribution that is observed? For the protozoa which were raised in laboratory conditions and identical medium it is more difficult (yet not impossible) to cite environmental factors. In a general way, however, in order to make a convincing case for a specific environmental factor, evidence must be provided showing that in a series of tests it has indeed the claimed effect. Otherwise it would be just an *ad hoc* explanation.

It is surprising that item 4 is almost never mentioned. In particular, we did not find it in the numerous papers of the 1910s and 1920s analyzing asexual reproduction. Yet, is it not a natural mechanism? It can easily account for continuous variability as described in Johannsen's paper because its randomness leads naturally to Gaussian distributions. Through the Central Limit theorem of probability the occurrence of a random discrepancy X_i at each step i of a multi-step pathway gives a nearly Gaussian distribution for the sum of the X_i (at least if the X_i are independent and have finite variance).

Through the hole and shaft mechanism described below item 4 can also account for variability by leaps, as happens for spine numbers or a similar effect for tentacle numbers in Lashley [20].

In principle if the manufacturing process is known it should be possible to compute and predict the variability of the output (except if butterfly effects play a major role). In other words, this framework can really be tested. Although in the present paper we limited ourselves to qualitative or semi-quantitative tests, subsequently it should be possible to find cases simple enough to allow modeling.

1.12. Outline of the paper

The paper proceeds through the following steps.

(1) First, we explain why random output fluctuations are inevitable in any production process. It is only thanks to a sound management of defects that an assemblage of several (defective) parts can be made workable. Depending on the specific industry, those management systems use different ways. We will focus on the tolerance system in use for mechanical systems because it is probably the easiest to understand.

(2) Secondly, we explain in what respects the two phases of human mortality, the "wear-in" and "wear-out" phases, bear close resemblance with the failure modes defined in reliability engineering.

(3) If simple technical devices can give us a better understanding of how to achieve minimal manufacturing defects, is it not natural to try the same approach for living systems? For instance, is the shape of the age-dependent infant mortality of simple living systems similar to or different from that of humans? This leads us in our conclusion to outline an agenda of cross-species investigations.

2. Fault-tolerant design

In order to make industrial production able to cope with output discrepancies in the supply chain appropriate systems have been developed. In the following subsection we explain briefly the tolerance system for mechanical devices. In recent decades much attention has also been given to electronic semiconductor systems because of the high complexity reached by such systems which may have millions (or even billions) of components [21]. In a broad way, the purpose is always the same and can well be summarized by the title of a paper written by John Von Neumann in 1952 (and published four years later) namely: "Synthesis of reliable organisms from unreliable components" [22].

2.1. Tolerance issues in the production of mechanical devices

First of all, it should be realized that mechanical operations involve inherent output variations. This was already mentioned earlier in an informal way; let us see more precisely how the tolerance system can deal with it.

Two holes made on a lathe with the same drill bit (say of 10 mm diameter) in an aluminum cylinder will in fact not have the same diameter. The boring operation will introduce a small but unavoidable random error. For instance, the diameter of the holes may be 10.003 mm and 9.996 mm respectively; naturally, the measurement introduces an additional uncertainty which will be ignored here for the sake of simplicity.

One may think that this small difference is of little importance but suppose that this hole is destined to receive a shaft which has a diameter of 10.000 mm. This will be possible for hole 1 but not for hole 2. In short, even small discrepancies may prevent assemblage.

[14] This statement just results from basic probability theory. Peto's paradox (namely that cancer incidence does not increase with the number of cells) relies on what happens not at cell level but at the level of the organism ("Why do not all whales have cancer?"). A mutated cell will lead to cancer only if it is not removed by the immune system.

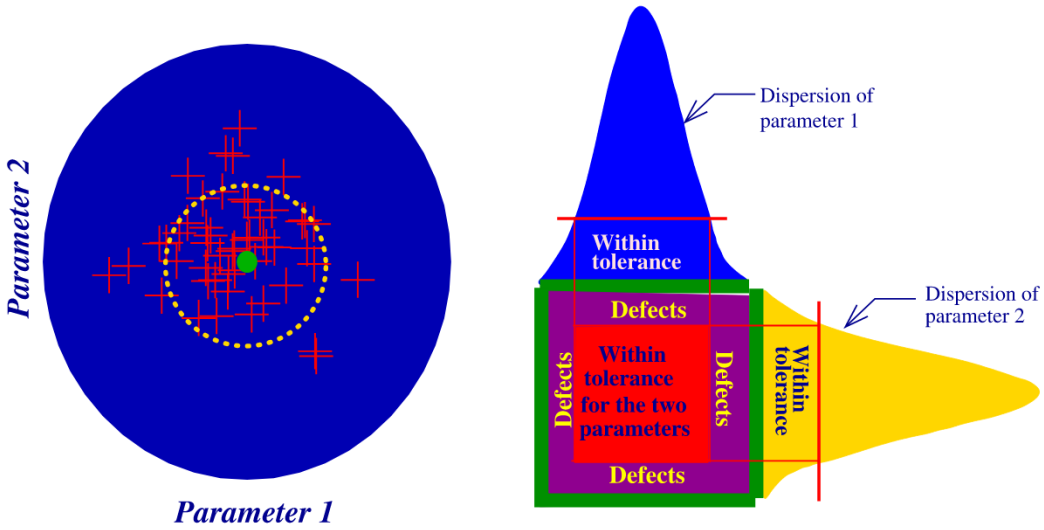

Fig. 2. Within and out of tolerance areas in the case of a process depending on two parameters. In this schematic representation it is assumed that a process depends simultaneously on two parameters, each of which has a Gaussian distribution. The green dot represents the (optimal) design values of each parameter. As illustrations one can mention the following cases. (i) The green dot corresponds to the ideal center of a hole that is drilled into an aluminum cylinder. Actual centers in 50 successive realizations are represented by the red crosses. Although never exactly at the design location, the effective centers may be close to it and fall within the tolerance domain represented in yellow (it was drawn as a circle for the sake of simplicity but in a general way it is an ellipse). (ii) For a chemical reaction, parameter 1 may be the concentration of one component and parameter 2 the concentration of the other. Then, the green dot corresponds to the optimum concentrations. For the process to unfold successfully both parameters must be within tolerance which means that all cases which fall in the magenta region will not work well and may lead to defects. For a process which has more than two parameters the acceptable zone would be reduced even further. Such additional parameters could be for instance the temperature and pH.

As already mentioned, in embryo-genesis there is a somewhat similar problem when two separate sheets are expected to join. In such cases even a small discrepancy in growth velocities may disrupt normal closure. This may create a defect of the neural tube which results in a birth abnormality called "Spina bifida", a Latin expression which means "spine split in two". Similarly, disruption of the closure of the left and right facial sheets may result in what is called a cleft lip and cleft palate. We come back to this point below.

A related case is the genesis of the furcula. In humans the furcula consists of two separate bones called clavicles or collarbones. On the contrary in birds it is a single V shaped bone called furcula (latin for small fork) or wishbone. Located in the upper chest of birds it is an essential structural element which allows them to move their wings; it also acts as a mechanical spring during flight. On day 13 of the 21-day long embryogenesis of chicks the left and right collar bones meet and close together to form the furcula. It can be predicted that even small discrepancies can prevent good working of this critical element.

2.2. The tolerance system as a way to mitigate the effects of manufacturing defects

Mechanical engineers have developed a system of standardized *tolerances*. In this context a tolerance is a specification which gives not only the nominal dimension but also the allowed margin. As an example, for the previous hole, the specification would be: 10+0.015−0 mm, meaning that it may be up to 0.015 mm larger than the nominal dimension, but 0 mm smaller (that is to say it should not be smaller than 10 mm).

The task of the engineer is to give for every dimensions appropriate tolerances so that, if respected, the device will work. For each separate part the technician who makes it will check whether or not it is "within tolerances". If it is not, it will be discarded and replaced by a suitable one.

There are similar tolerance systems for electrical elements such as capacitors or resistances. The specification (often written on the element itself) may indicate the nominal value (e.g. 100Ω), the margin of error (e.g. $\pm 1\%$), the temperature range (e.g. 5 to 35 Celsius degrees).

One could summarize the specification procedure by saying that the science of engineering is to make working devices with spare parts which, strictly speaking, are all defective in the sense that their values differ from the nominal values (but are within tolerance margins). This mechanical example is useful because it allows a clear understanding of the problem but since living organisms are not made with nuts and bolts, nor with resistors, one must explain how this should be adapted.

2.3. Output dispersion in biological systems

At first sight one may think that the two cells produced in the fission of a parent cell are exactly identical. The previous discussion suggests that in fact they are not, but does not explain the why and how. Basically, biological processes consist of a succession of physico-chemical reactions. In order to give an intuitive feeling of why such reactions are sensitive even to fairly small condition changes we will make three points. (i) First we emphasize the relatively high frequency of errors in protein folding. (ii) Secondly, we explain how spatial factors play a great role in reactions involving enzymes. (iii) Thirdly, we consider a simple reaction whose high sensitivity to temperature may be familiar to many readers.

(1) It has been recognized that "errors arise at all steps of protein synthesis, from transcription to protein folding, and have widespread phenotypic consequences". Due particularly to the "fragility" of protein folding mechanisms "errors in protein synthesis are orders of magnitude more frequent than DNA-replication errors" [10]. This review paper contains a table which lists a number of errors along with their estimated frequency.

(2) One hallmark of the present paper is to emphasize the role of geometrical and positional factors. Here is another case of that kind. We know that enzymes (most enzymes are special kinds of proteins) act as catalysts of chemical reactions. In fact, they are highly sophisticated catalysts in the sense that they can play this role not only for one specific reaction but for several. In addition, their activity can be modulated according to needs. In other words, they are a kind of multipurpose control station, somehow like the control room of a power plant. The multipurpose capability comes from the fact that at their surface they have several so-called active sites where the reaction will take place; each active site is coupled with a so-called allosteric (meaning "other place") site which will bind with control molecules that can be either activators or inhibitors. Needless to say, if a control molecule is attached near but somewhat off the right location its regulation function will not be well implemented. With allosteric sites that are particularly cramped there can be situations similar to the hole and shaft case where even a small shift can greatly affect the enzyme and therefore the reaction that it is supposed to catalyze. To make things even more complicated, one should add that many enzymes do not work well if they are not bound to helper molecules called cofactors.

(3) Our third illustration is a process which may be familiar to many readers. As is well known, a mayonnaise is made by slowly adding oil to egg yolk, while whisking vigorously with a fork. An emulsion will form made of small oil droplets. These droplets are strongly held together by van der Waals intermolecular attraction forces which cause the high viscosity of mayonnaise [23]. Addition of mustard contributes to the taste and further stabilizes the emulsion.

This, at least, is the theory.

In fact, the operation may fail (i.e. no emulsion forms) for various reasons.

(i) It fails when the oil is added too quickly.

(ii) It fails when the temperature of the oil is too high; as a matter of fact, it works best when the oil and egg come directly from the refrigerator.

(iii) Another reason for failure may be the presence on the fork of traces of a product preventing the formation of the emulsion.

In short, we have here a simple physico-chemical process which has fairly strict tolerance specifications. If two or several processes are involved either successively or at the same time, the tolerance area is further reduced (Fig. 2).

3. Salient features of embryonic mortality

In previous sections it was suggested that a manufacturing process which involves major innovations is more prone to faults than mere cell reproduction by fission. That is why, for instance, the transition from stem cells to fully differentiated cells is a more challenging task than duplication.

The process by far the most innovative is the transition from a zygote, i.e. a fertilized cell, to a fully developed embryo. Within a fairly short fraction of the order of 10% of the embryonic period, a completely new organism will be created and each step is highly dependent upon the satisfactory outcome of previous steps. In other words, this is a critical development process in which major faults are expected to occur with significant probability.

3.1. Implication of geometrical abnormalities for development of the embryo

Fig. 3a shows *position anomalies* occurring in the early steps of embryogenesis and Fig. 3b indicates that they have adverse implications as revealed by the fall in hatching rates.

3.2. Age-dependent embryonic mortality

In demography age-specific death rates are a key-variable.[15] In the embryonic phase they are paralleled by mortality rates as a function of post-fertilization age which, therefore, should also be seen as a key-variable. Curiously, it attract little attention so far; as a result, such data are available for only few species. Fig. 3c presents data obtained by three high-accuracy studies for bird and fish species. The graph also shows human data, albeit with the drawback of starting 4 weeks after conception.

[15] From a physical perspective the resolution of demographic phenomena into age-specific components is similar to frequency analysis of physical phenomena; for more details see Berrut et al. [29].

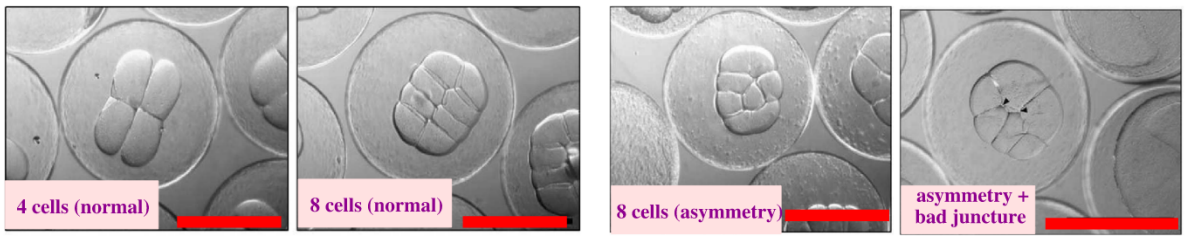

Fig. 3a. Cleavage abnormalities in haddock embryos. Examples of abnormalities occurring in the first steps of embryogenesis. The growth process starts with one fertilized cell, then subsequent steps every 20 mn with 2, 4, 8, 16,... cells. The pictures show that early defects can occur already in the 8-cell step. Normal development is shown on the left-hand side and abnormal development on the right-hand side. The red segment corresponds to 1 mm. Apart from the two cases shown here three other sorts of abnormalities are described in the same paper, namely (i) unequal sizes of the cells (ii) cellular outcrops where one or two cells protrude from the main group of cells. (iii) Separation of the 8 cells into two disconnected sets. In the following figure it is shown that such abnormalities result in lower hatching rates that is to say in increased embryonic mortality.
Source: Adapted from Rideout et al. [24, p. 219]

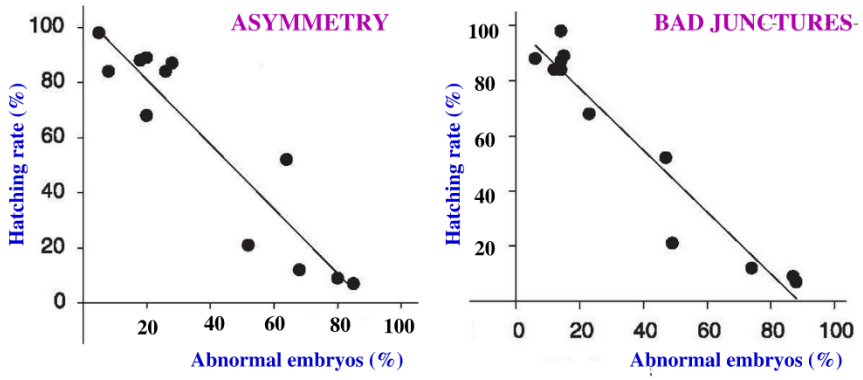

Fig. 3b. Hatching rates for embryos involving malformations. Hatching rates were measured for 12 samples containing various proportions of defective embryos. The coefficients of linear correlation are equal to $r = 0.93$ and $r = 0.96$, respectively. Similar correlations are obtained for size and outcrop anomalies.
Source: Adapted from Rideout et al. [24, p. 222]

3.3. General observations about embryonic mortality

What can be said about the role of mutations and environmental factors?

For the animal experiments described in Fig. 3c all embryos were raised in identical conditions so that exogenous factors can hardly explain why some embryos are affected by severe anomalies while others are not.

Mutations are certainly responsible for some anomalies but under the assumption of a uniform mutation rate it seems difficult to explain the huge changes affecting the death rate. For turkey or chicken eggs why should there be more lethal mutations on day 1 than on day 11?

For all four species, there is a sharp fall of the death rate between fertilization and the subsequent leveling off. For the turkey, perch and human cases the death rate is divided by a factor of about one hundred whereas for chicken the factor is about 30. However this last factor is affected by a substantial uncertainty because of the small numbers of deaths; indeed, between days 8 and 14 the daily death numbers are all smaller than 6 with three of them being zero or one.[16]

The fact that for the avian cases there is a second peak on the right-hand side whereas no similar peak appears in the two other cases is due to the fact that birds have to pierce the shell of their eggs which is a difficult task. If early neonatal death rates would be included into the embryonic phase there would also be a left-hand side peak in the perch and human cases. In other words, this difference is related to how one defines the end of embryogenesis.

As a last point we wish to compare the absolute magnitude of the death rates at the beginning of the embryo development. For this comparison we leave apart the human case for reasons which are explained below.

For turkeys the first data point which is an average for the first three days stands at 14 per day and per 1000 fertile eggs. For chicken the average for the first three days stands at 22 which is close.

For the European perch the data point for the first day stands at 167 that is to say about 10 times higher than for the birds in 3 days. The interpretation of this difference remains an open question at this point.

[16] This is in spite of the fact that the experiment involved 3240 eggs and that 471 of these embryos died. As the turkey experiment involved 10 times more eggs its results are more reliable.

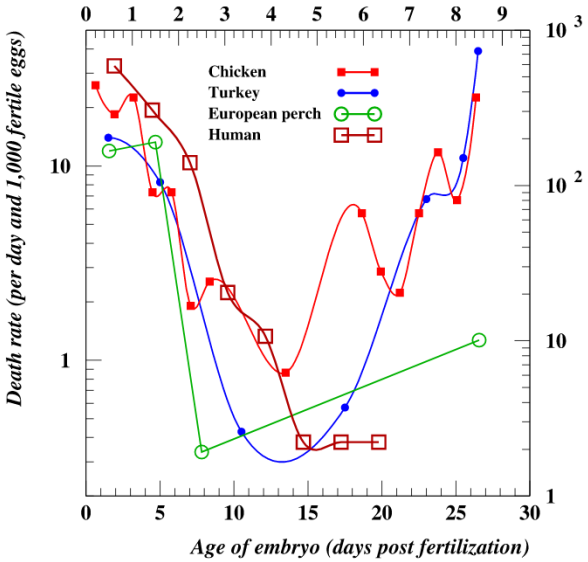

Fig. 3c. Embryonic mortality rates. The bottom and left-hand side scales are for birds. The top and right-hand side scales are for fish (ages are also expressed in days). The scales for humans (not shown) are as follows: the age scale starts with the 4–7 weeks gestational age interval and ends at 50 weeks. The vertical scale (expressed in rates per 1000 pregnancies) starts at 2 and ends at 150. Note that the data provided by vital statistics agencies usually start only at 20 weeks. The present data for the intervals between 4 and 20 weeks were obtained through a special study covering a 4-year period (1953–1956). Note that the age scale of the chicken case has been extended from 21 to 24 days to facilitate the comparison with the turkey case. Note that the perch curve is made of straight lines because there are too few data points to use a smoothing option.
Source: Sources of the data: Chicken (broiler): Peñuela and Hernandez [25, p. 6505], number of fertilized eggs (n) = 3146; turkey: Fairchild et al. [26, p. 262], $n = 51, 764$; European perch: Alix [27, p. 161], $n = 13, 500$; humans: French and Bierman [28, p. 840, 844], $n = 3083$.

3.4. Avian species

To the two avian cases shown in Fig. 3c one can add that a similar pattern was observed for several other avian species, e.g. pigeons, doves, ducks, grouse, pheasants and quail [30].

The fact that some of these deaths are due to fairly random conditions can be illustrated by the case of malpositions. It has been observed that one half of all chick embryos which die between day 18 and 20 were in abnormal positions [31]. In order to understand the reason one should recall that the lungs of chicks start to work shortly before they begin to break the shell of the egg. However, to make that possible they must have access to the air cell which is on the blunt tip of the egg. If for some reason their head cannot move in time to the right location the chicks will die. Moreover, to pierce the eggshell is quite a challenge.[17] If, for some reason, the eggshell is too hard or too thick the chick may be unable to break it.

3.5. Fish species

The embryonic phase of fish can be studied easily due to the fact that the fertilization of the eggs occurs outside of the body of the female. For that reason one can get reliable death data even for the very early part of the cycle. For instance, for zebrafish as the first division of the fertilized embryo occurs less than an hour after fertilization one should be able to get hourly death rates. Unfortunately, such investigations did not attract much attention so far. To our best knowledge the case of the European perch described in Fig. 3c is an unparalleled study of fish embryonic mortality.

3.6. Human fetal deaths

The study described in French and Bierman [28] took place in the island of Kauai in the state of Hawaii. During the four years of the study there were 3083 pregnancies, 273 fetal deaths and 2777 live births. These are of course small numbers due to the fact that the island's population was only 30,000. The reason for doing the study in this place was the existence of a well organized network of medical personnel.

Very early fetal deaths can only be noticed by the women themselves. That is why this part of the death rate curve must be recorded through special surveys involving a devoted network of physicians and medical personnel. Standard fetal death statistics as provided by hospitals include only pregnancies which lasted more than 20 weeks.

[17] For that purpose the chick is using a special "tool" in the form of a so-called egg-tooth which is a sharp temporary structure on the top of the beak. There is also a special "hatching muscle" which serves the purpose of activating the egg-tooth.

In the three other cases of Fig. 3c the procedure was to observe a sample of N eggs in the course of time and for each subsequent day to record the number of surviving embryos. Clearly, it was not possible to use the same procedure here. As pregnancies and fetal deaths were recorded in a continuous way the whole process required more intricate and less transparent computations.

3.7. How can one explain that the death rate is highest at the beginning of embryogenesis?

Here is a tentative interpretation of the fact observed in Fig. 3c that the death rate is highest on the first day of the embryogenesis.

In principle the organism of the mother produces embryos equipped with all that they need to grow. But, as for any real process, there are necessarily faults and defects. The embryos in which some important ingredients are missing will be unable to grow and instead will die. As these faulty embryo are gradually eliminated the death rate will decrease just as observed.

At present this mechanism is purely speculative but the interesting point is that it can be tested. How?

Consider for instance the case of zebrafish embryos. Two hours after fertilization the embryo has about 64 cells. If the embryo is able to reach this point it means that it is well equipped, at least for the cleavage phase. In contrast, one would expect the faulty embryos to be eliminated very shortly after the beginning of the embryogenesis. This means that the death rate should be highest in the very first hours. In other words, this explanation can be tested by measuring the embryonic death rate every 2 or 3 h during the first 24 h.

3.8. A conjecture about embryogenesis in unicellular organisms

In unicellular organisms is there a process similar to embryogenesis which precedes the birth of a new organism? Formally no, but functionally yes. For instance in the prokaryotic bacterium *Caulobacter crescentus* the initiation of replication starts some 2 h before division actually occurs [32, p. 2145]. This phase (which consists of successive so-called G_1, S and G_2 transitions) can be considered as a kind of embryogenesis during which the new organism is made ready for autonomous survival.

Naturally, the success rate of the complex transformations which take place is certainly not 100.00%. For instance, it has been shown [33] that hyper expression of one gene (named *podJ*) involved in a crucial transition at the beginning of the replication process causes a lethal cell division defect. Thus, it is conceivable that random fluctuations in the concentration of this protein will lead to a percentage of failures.

This means that, in the same way as there is an embryonic death rate, there will be a predivisional death rate. The magnitude of this death rate will give an estimate of the sensitivity of the process to random variability. The more sharp requirements are included in the design of the process, the higher the expected failure rate.

In the wake of the division, as indeed in a more general way after any major transition, one expects a phase of infant mortality during which the death rate of the daughter organisms will start from an inflated level and then decrease as the screening progresses. Those organisms for which the replication process has been carried out to its end but which nevertheless are not completely fit for an autonomous existence, will die.

3.9. Influence of temperature on hatching rate

Fig. 3d shows a striking influence of temperature on the average mortality rate during the 21-day long of the embryonic phase of chicks. In terms of hatching rate which is perhaps more suggestive (but less appropriate for cross-species comparison) there is an increase from 10% at 35.8 degrees to 88% at 38.1 degrees and then a fall to 50% at 39.8 degrees.

It can of course be argued that the temperature is an environmental parameter but this is just a label and would not help to explain the behavior seen in Fig. 3d. It is clear that it is only through a better understanding of the manufacturing process that we can hope to predict the shape of the mortality curve; needless to say, the temperature is an essential variable in this process.

4. Salient features of the two phases of human mortality

Our main goal in this section is to show that the curves of age-specific infant mortality rates provide, so to say, a global quantitative summary of the various congenital anomalies that appear in the embryonic phase.

4.1. Human infant mortality for all causes of death

As our starting point we consider infant death rate curves for humans as shown in Fig. 4a,b.[18] Three striking features of infant mortality rates appear in Fig. 4a,b but before we describe them in detail we wish to attract the attention of readers to two aspects. (i) Fig. 4a shows that the death rates exhibit essentially no random fluctuations. (ii) Fig. 4c shows that the

[18] More details about infant mortality can be found in Berrut et al. [35].

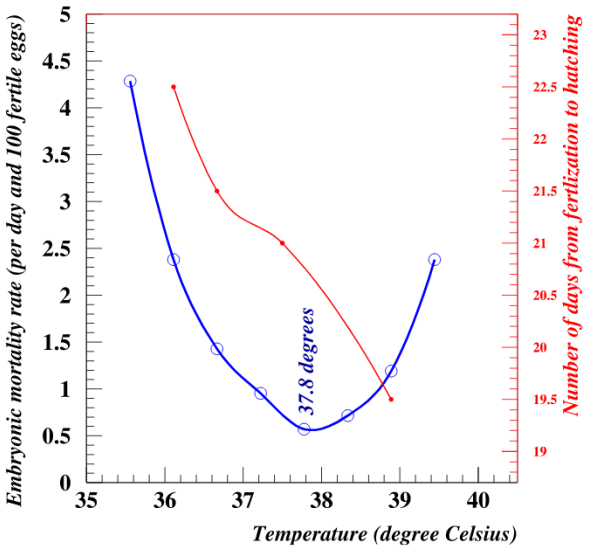

Fig. 3d. Average embryonic mortality rate for chicks from fertilization to hatching. Apart from the mortality rate, the graph shows also the length of the embryonic phase. On account of the fact that the speed of most chemical reactions increases with temperature one is not surprised by the shortening of the embryonic phase. On the contrary, the fact that the mortality rate exhibits a sharp minimum requires an explanation. A good test of our understanding of this manufacturing process will be our ability to predict (at least approximately) the optimal temperature.
Source: Source of the data: ISA Institut de Sélection Animale [34].

pattern of death rates remains fairly stable even when the death rate level changes considerably as happened between 1923 and 1960. Moreover, an examination across several countries shows that these curves remain much the same in all developed countries. As an illustration, one may look at the death rate curves for the UK shown in Berrut et al. [35].

One may think that the first point is hardly surprising because the death rate is an average over a large sample comprising thousands of deaths for each age interval. However, averaging alone cannot explain the absence of fluctuations as is demonstrated by the fact that weekly or monthly death rate curves show fairly large fluctuations. This suggests that changes with age are more stable than changes in the course of (calendar) time. As a matter of fact, it will be seen in Bois et al. [36] that this stability is greater for young-age deaths than for old-age deaths.

Now we describe the three salient features of the shape of the infant death rate curves.

(**1**) **Birth-time spike**

The most impressive feature is certainly the very sharp spike which coincides with birth. It means that the death rate is high immediately after birth but decreases rapidly in subsequent days and weeks.

(**2**) **Power law fall**

In Fig. 4a this decrease seems to level off after the age of 60 days. In fact, the decrease does not stop but simply becomes slower.[19] This fall is described by a power law [20] which continues until the age of 3600 days that is to say about 10 years. If one considers that the maximum life span is about $T_{\max} = 100$ years this corresponds to 10% of $T_{\max}$. After the age of 10 years the death rate increases steadily and exponentially up to $T_{\max}$ in accordance with Gompertz's law.

Although in medical language, infant mortality is understood as the first year after birth, in the present paper "infant mortality" refers to the whole phase during which the death rate decreases. This definition follows a well established usage in reliability science.

(**3**) **Exponent of the power law**

During the infant mortality phase, the human death rate[21] decreases in an hyperbolic way of the form: $x(t) = A/t^{\gamma}$ where the exponent γ is of the order of 1.

By saying that γ is "of the order of 1" we mean that (as shown in Fig. 4a,b) it is comprised between 0.6 and 1. In contrast, for some species it can be as low as 0.5 (see crocodilians in Bois et al. 2019a, Fig. 2) or as high as 3.5 (see fish in Bois et al. 2019a, Fig. 5a,b).

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19 By this expression we mean that a fall from 1000 to 100 will take place between day 1.5 and 7, whereas from 10 to 1 it will take from day 150 to day 700 (approximately).

20 Although the distinction between power law and exponential is well known in biology it is not seen in the same way as in physics. It is of course obvious that an exponential falls off faster than a power law, but one must realize how massive the difference is.

$$y_1 = 1/x, \quad y_2 = \exp(-x) \ : x = 10 \ \rightarrow \ y_1 = 0.1, \ y_2 = 0.000045$$

This makes the two functions really different in nature. For instance, the exponential form of Gompertz's law *absolutely* forbids anybody to reach the age of 130 years.

21 Defined as: $\mu_b = (1/x_0)\Delta x/\Delta t$, where x_0 = number of life births, Δx = number of deaths in the age interval Δt.

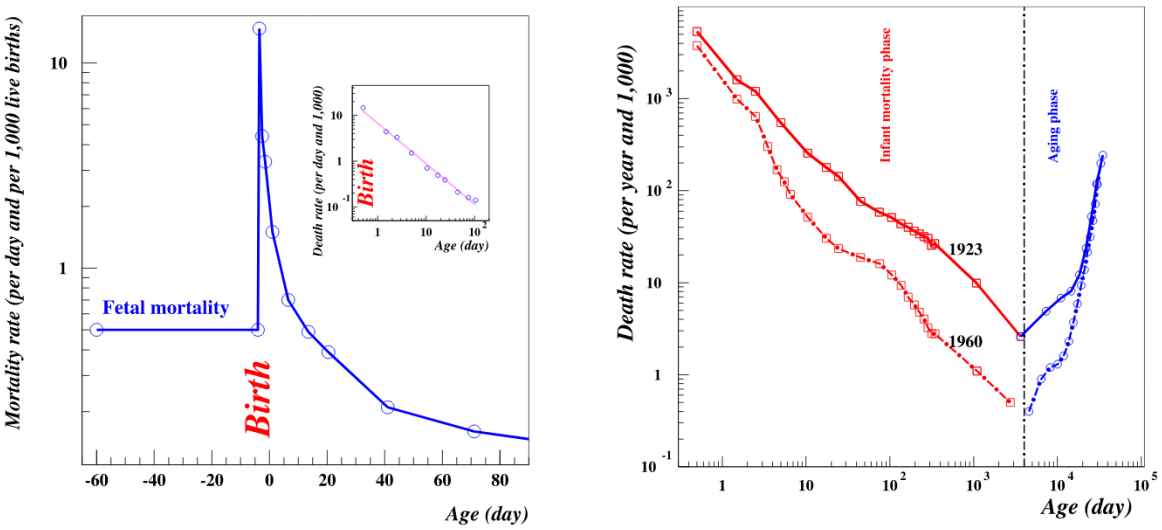

Fig. 4a,b. Infant and adult mortality rates for humans (United States). (a) is for 1923 in the US and the inset is for the same data in log–log coordinates. Fetal mortality corresponds to the average level of late fetal mortality (6 to 9 months pregnancy). (b) extends until 30,000 days which represents 82 years. The three main features of infant mortality are the following: (i) The sharp spike at birth. (ii) The decrease of infant mortality rate between birth and the age of 10 followed by subsequent increase. (iii) The fact that, as a function of age t, the decrease follows an hyperbolic law of the form: $\mu = A/t^{\gamma}$ with γ of the order of 1 (a more complete discussion can be found in the text). Note that despite the huge fall of the death rate between 1923 and 1960 the structure of the two phases did not change much. In 1923 $\gamma = 0.65 \pm 0.04$, whereas in 1960: $\gamma = 1.01 \pm 0.08$ (the error bars are for a confidence level of 95%). The change in the slope from 1923 to 1960 is due to the fact that early mortality is almost time independent (because mostly due to malformations) whereas the mortality at the age of 10 has decreased considerably. In the interval (0, 10) the infant mortality rate is defined as: $\mu_b = (1/x_0)\Delta x/\Delta t$, where x_0 = number of live births, Δx = number of deaths in the age interval Δt; this definition is standard for the interval (0, 1) but here we extend it to the age interval (0, 10). In the expression of the adult mortality rate μ, the denominator x_0 is replaced by the number $x(t)$ of individuals alive at the beginning of the age interval Δt. Actually, as long as the total infant deaths remain under 10%, using the adult definition at all ages would not make much difference because in this case the infant age groups are anyway close to x_0. A last comment is in order to say that in the present paper the expressions "death rate" and "mortality rate" are used as synonyms; sometimes "death" is preferred to "mortality" just because it is shorter (that is why it is used in the small inset graph).
Source: 1923 (a) Under one year: Linder and Grove [37, p. 574], (b) Over one year: Linder and Grove [37, p. 150] (gives in fact 1920); 1960 (a) Under one year: Grove and Hetzel [38, p. 210–211], (b) Over one year: Grove and Hetzel [38, p. 318].

In the case of humans the variations of γ with the level of development of countries is easy to understand through the following argument introduced in Richmond and Roehner [39].

- The mortality rate immediately after birth is practically independent of development level because it is determined by lethal birth defects.
- In addition, one can accept the rule that the decrease with age is a power law because this is confirmed by all available evidence.
- Finally broad empirical evidence (provided for instance by the "Global Burden of Disease" study,[22]) Wang et al. [40] show that the mortality rate at the age of 10 is closely connected with the level of development. In developed countries between the age of 10 and 30, accidental factors (e.g. traffic accidents or suicides), play a leading role. Suicide, for instance, is one of the main causes of death among young people but this holds only because the other death rates are very low.

Thus, in a log–log plot, one has to draw a straight line between a fixed point on the left (namely the mortality at birth) and a data-point at age 10 which is lower in countries with higher levels of development. Thus, this straight line will be steeper, and the exponent γ higher, as development progresses. This is indeed what was seen in Fig. 4a,b from 1923 to 1960 when the exponent increased from 0.65 to 1.

4.2. The age of 10 seen as an equilibrium point between screening and wear-out

If one attributes the downward part of the mortality curve to a screening process through which individuals with congenital malformations are eliminated and its upward part to wear-out, it makes little sense to assume that the first effect stops at the age of 10 while the second starts at that age. Certainly the screening continues after 10 and the wear-out starts immediately after birth. In this perspective, 10 becomes the equilibrium point between the two effects.

22 This study has involved several hundred researchers and it covers the whole world. In contrast with other global studies, it contains a detailed discussion of the precautions that must be taken when using data generated by statistical organizations which do not all have the same level of reliability and accuracy. For instance, broad and ill-defined causes of death (called "garbage codes") may exist. One such example is "injuries" which, apart from diseases, can be almost anything. Wang et al. [40] also emphasize the need to pay more attention on the sources of mortality during adolescence.

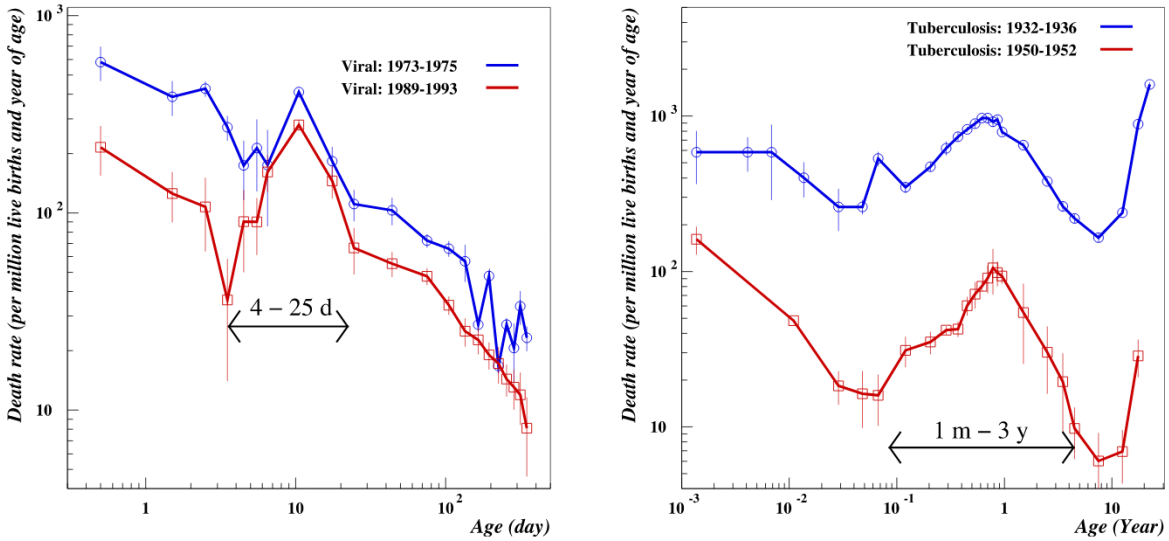

Fig. 4c,d. Infant mortality rates for viral diseases versus tuberculosis in the United States. Left Although there is a general diminution of the death rate from 1973–1975 to 1989–1993 the peak of the first curve (in blue) has an amplitude (ratio of top rate to base rate) of 2 whereas the second curve (in red) has an amplitude of 5. The error bars give the standard deviation of the average of individual years in the respective age intervals. **Right** One observes the same phenomenon as in the graph for viral diseases, namely an overall diminution coupled with a higher peak in the more recent time interval: for 1932–1936 the peak has an amplitude of 3 whereas for 1950–1952 its amplitude is 6.5. It should be noted that these peaks are also visible on the total mortality curves but in attenuated form which means that one needs high accuracy measurements to detect them.
Source: Vital Statistics for the United States for the appropriate years; Berrut et al. [29]

4.3. Infant mortality for specific causes of death

The graphs of Fig. 4c,d show infant mortality for specific causes of death, namely viral and bacterial diseases (of which tuberculosis was the most important instance in the early 20th century). Figs. 4b, 4c,d show a broad downward trend but in addition for specific age intervals there are peaks denoting mortality surges. In fact, these peaks are also visible on the "all causes" curves but only with poor accuracy because they are overshadowed by the general trend of all other causes.

The reason for these peaks is not yet clear but it is likely that they relate to the gradual establishment of the immune system. Shortly after birth the newborn is protected by the antibodies contained in the breast milk of the mother but this protection is gradually replaced by the child's own immune system. Moreover, the immunity provided by the mother first during pregnancy and then shortly after birth depends on the diseases that the immune system of the mother had to face.

In other words, these surges in infant mortality can tell us something about special events in infant development that would not be visible otherwise.

5. Conclusion

5.1. Main results

The considerable variety of birth defects, whether lethal or non-lethal, attests that control mechanisms can be overwhelmed in many ways. However, the relatively low frequency of each of these defects (mostly under 1 per 1000) attests that most of the time the "manufacturing process" works fairly well.

In this paper we have introduced the idea of a third source of congenital anomalies besides the genetic and environmental factors. It was called "manufacturing dispersion" because it consists in the accumulation of small output defects in the successive steps of a development process. Such a mechanism was shown to be responsible for a substantial variability even with the two other factors are inactive. This would solve the mystery of the large proportion of defects for which no specific source can be identified (as noted at the beginning of the paper).

We have described a number of circumstances which are likely to amplify output dispersion: complex organs, processes which require perfect synchronization in time and space, rapid and drastic transformations.

The observation of unexplained discordances in phenotypic expressions, as reported by many authors (see for instance [41]), has led to the introduction of notions such as:

- "micro-heterogeneity",
- "genetic mosaicism",

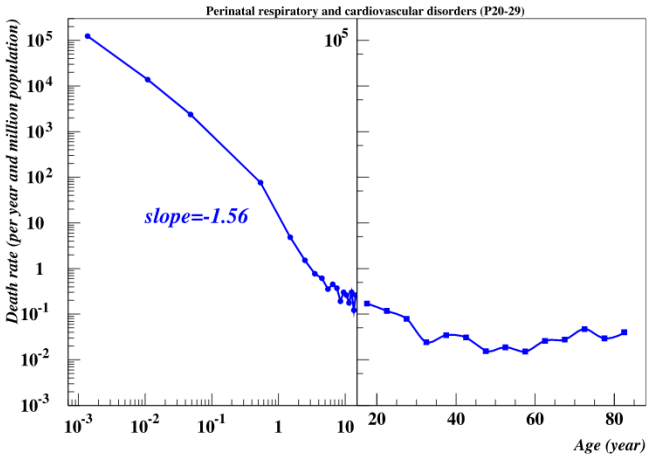

Fig. 5. Infant and adult mortality due to lung and heart congenital abnormalities in the United States. There are two noteworthy features. (i) The high slope of 1.56 is associated with a high initial mortality rate (in the first year it is 168 times higher than for spina bifida) and reveals a drastic screening process. (ii) As a result, this cause of death is nearly eliminated which explains that the adult death rate is not increasing with age but instead fluctuates more or less randomly at a very low level of less than 100 annual deaths.
Source: CDC Wonder: Detailed mortality 1999–2017.

- "noisy gene expression" or "phenotypic noise",
- "stochasticity at the biochemical level".

Because these notions have no clearly defined operational basis they can hardly lead to testable predictions. If the source of stochasticity is not defined no rule can be derived; in other words, without a physical basis the word stochastic will just mean irregular and chaotic, which is not of great help.

Clearly one would like to get a better understanding of the basic mechanisms of manufacturing dispersion. It is for that purpose that in a forthcoming paper [42] we propose two simple physical models which provide a clearer insight than *in vivo* biological organisms.

5.2. Rationale for cross species comparisons

The dispersion hypothesis led to the prediction that "simple" organisms should have less lethal congenital anomalies than complex organisms like mammals. As an illustration consider the following example.

In humans, within a few days after birth, heart and lungs defects are the main causes of death (see Fig. 5); lung problems are particularly critical for preterm newborns.

In contrast, for rotifers these two causes are completely non-existent for the simple reason that rotifers have neither heart nor lungs. Because of their size (about 0.2 mm in length and 0.03 mm in diameter) rotifers, like all other aquatic organisms of similar size or smaller, receive their oxygen by diffusion through their skin. There is of course a similar diffusion process for larger animals, but whereas the concentration jump, Δc, is the same, the skin thickness, Δx, may be 100 times larger, thus giving a diffusion gradient, $\Delta c/\Delta x$ some 100 times smaller. Size also makes blood useless because oxygen can be brought by diffusion to all parts of the body.

In short, for rotifers one does not expect the kind of sharp peak immediately after birth as observed for humans. Is there nevertheless an infant mortality phase during which the death rate decreases? Only observation can tell us. That is why rotifer mortality will be studied in a companion paper [36].

Incidentally, it can be observed that the diffusion mechanism works not only for microscopic organisms but also for centimeter-size organisms on the condition that they are formed of thin layers. That is the case for: (i) sponges consisting of a single cell layer or (ii) jelly fish whose body is a layer not more than a few cells thick. In all these organisms gases, nutrients, and wastes are exchanged by diffusion. Thus, as a conjecture, one would expect their infant mortality curve to start similarly as the one of rotifers.

More broadly, it is in order to test such predictions that we started a research program consisting in the measurement of infant mortality across species.

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Appendix. Estimating the strength of genetic factors

It is probably not far from the truth to say that nowadays some 90% of the research papers in biology are to some extent focused on genetics. This is surprising because, as explained in a review paper published in the "New York Times" [43], demographic and epidemiological research shows that for most human characteristics (e.g. lifespan or diseases) there is only a loose genetic influence.

Here we are interested in birth defects. Because they are not affected by all life incidents (which differ from person to person) one may think that there is a firmer ground for genetic influence. Currently, it seems to be a well accepted axiom that most malformations have a genetic origin. At least this is the implication of papers which, for all separate variants of finger malformations, lists the genes which seem responsible. Under such an assumption, monozygotic twins should have the same malformations. We will see below that this is far from true.

Before focusing on the twin methodology, let us briefly examine two related aspects of birth anomalies.

A.1. Mutations and repair mechanisms

In a living organism harmful mutations can occur at three levels. (i) Germ cells. (ii) Stem cells, i.e. cells not yet differentiated into specific organ types. (iii) Fully functional differentiated cells existing in various organs. The last two types are called somatic mutations for they are not passed on to children.

In a long term perspective the most serious cause of concern are of course the germ cell mutations because, unless there is a repair mechanism, they will be passed over from generation to generation and will accumulate.[23] So, the existence of effective repair mechanisms has been a natural assumption among biologists long before it was eventually demonstrated in a work honored by a Nobel award in 2015.

A.2. Birth defects in successive family generations

The observations based on twins are fairly "clean" and easy to interpret. Unfortunately the numbers of cases are rather limited. If a defect can be transmitted genetically one would expect it to be more frequent among the successive generations of the families where it appears than in the general population. Needless to say, such observations are not easy to interpret for usually family members also share similar environment conditions. Although less easy to interpret, such studies can give additional information. For instance, Koskimies et al. [44] is a study of hand and arm abnormalities which covers all 753,342 births which occurred in Finland from 1993 to 2005. 419 cases of upper limb defects were identified. The paper makes two interesting points.

(1) The study reveals that the infant mortality (for age under 1 year) of these 419 children was 137 per 1000 live births which is 41 times higher than the infant mortality in the general population, namely 3.7 per 1000 births. As arm or hand defects are not in themselves a cause of death, it means that these children had other birth defects. This was confirmed by the fact that additional defects were indeed found in 60% of them (the remaining 40% may have had defects difficult to detect). This observation speaks against the vision (presented for instanced in Ahmed et al. 2017) in which specific gene anomalies would be responsible for different variants of finger malformations. A more realistic view is that "something" went wrong in embryogenesis in the weeks during which upper limbs form and that this problem also affected other organs (e.g. cardiac and renal) which appear in the same development stage.

(e) Of the 419 children, 9 (i.e. 2.1%) had relatives with an upper limb defect. Is this more than in the general population? The incidence in the general population was 0.52 per 1000 live births. For the purpose of comparison one needs to know the average number of relatives of each child. As this number is not given in the paper, let us assume 8 relatives on average. Under this assumption one gets an incidence rate of 3.3 per 1000 births in the 419 families.

However, this calculation involves births of parents and grand parents which have occurred a long time ago when the incidence may have been higher. One is led to the conclusion that the incidence in the families involving birth defects was higher than in the general population but not by much.

[23] There may be many external mutation factors but one that has existed without any doubt since the beginning of life on Earth consists in high energy cosmic rays.

Table A.1a
Twin variables for estimating the strength of genetic factors in malformation occurrences.

	MZ Concord. pairs c_m	MZ Discord. pairs d_m	MZ Ratio g_m	DZ Concord. pairs c_d	DZ Discord pairs d_d	DZ Ratio g_d	MZ/DZ $g' = g_m/g_d$
100% genetic	c_m	$d_m = 0$	$g_m = 1$	c_d	$d_d > 0$	$g_d < g_m$	$g' > 1$
0% genetic	Np^2	Np	$g_m = p$	Np^2	Np	$g_d = p$	$g' \simeq 1$

Notes: MZ means monozygotic (true twins) and it corresponds to the index m; DZ means dizygotic and it corresponds to the index d. N is the population of the sample of twins (MZ twins for the left-hand side, DZ twins for the right-hand side). "Concord." means "Concordant" (corresponds to the variable c). "Discord." means "Discordant" (corresponds to the variable d). Note that the signification of d depends on whether it is a variable (then it means "discordant") or an index (then it means "dizygotic"). As an example of the notations, the variable c_d represents "concordant pairs of dizygotic twins. g_m and g_d have the following definitions: $g_m = c_m/(c_m + d_m)$. $g_d = c_d/(c_d + d_d)$. p is the probability of the malformation in the general population; it is assumed that $p \ll 1$ (usually $p \simeq 10^{-3}$). High strength of genetic factors is associated with g_m close to 1 and g' higher than 1, whereas low strength is associated with g_m much smaller than 1 and g' close to 1.

A.3. The twin methodology for assessing the strength of genetic factors

A methodology based on twin data which permits to ascertain the role of genetic factors in the occurrence of malformations (or more generally of any disease or trait) has been developed by several authors, e.g. Hrubec and Neel [45] and Tishler and Carey [46]. However, as the method is used differently in each specific application, we summarize in this appendix the variables and reasoning which are most convenient for our purpose.

Before giving a formalized presentation for a large sample of twin pairs it may be useful to describe a specific case consisting in the occurrence of breast cancer in monozygotic twins. A team of Czech researchers followed 5 monozygotic pairs of twins over a long time period of up to two decades. They made the following observations [47].

- Pair 1 = (breast cancer at age 54 versus ovarian cancer at age 43)
- Pairs 2, 3, 4, 5 = (breast cancer at a median age of 44 versus no cancer)

Naturally, cancer is not a clear case because it occurs late in the course of life and can therefore involve many environmental factors. In what follows we focus mostly on birth defects.

The starting point is a dataset for a sample comprising M monozygotic (MZ) twins and D dizygotic (DZ) twins. Secondly, one focuses on the frequency of a specific congenital malformation. This leads to define and compute the following variables.

- Concordant pairs, i.e. pairs in which both twins have the malformation; we denote their number by c_m and c_d respectively for MZ and DZ twins.
- "Discordant" pairs, i.e. pairs in which one child has the malformation but not the other; we denote their number by d_m and d_d respectively for MZ and DZ twins.

In addition, we denote the probability of the malformation in the general population by p. A typical order of magnitude for p is 1 per 1000 that is to say: $p = 10^{-3}$.

Ideally, for a malformation that is 100% genetically determined, among MZ twins there should be no discordant pairs, i.e. $d_m = 0$. Thus, if we introduce the ratio $g_m = c_m/(c_m + d_m)$ it will be equal to 1.

In contrast, for DZ twins there may be some discordant pairs, i.e. $d_d > 0$. Thus, for $g_d = c_d/(c_d + d_d)$ one gets: $g_d < 1$, in other words: $g_d < g_m$; this last inequality is also expected to hold at least approximately for malformations in which genetic determination is less than 100%.

For a malformation which has no genetic basis at all, the probability for both twins to have it would be p^2, whereas the probability for only one having it would be: $p(1-p)$; as usually p is of the order of one per thousand the factor $1-p$ can be approximated by 1.Thus,

$$c_m = Mp^2,\ d_m = Mp \ \rightarrow\ g_m \simeq p^2/(p^2 + p) = p/(p + 1) \simeq p$$

Naturally, in this case the expectations for DZ twins are the same as for MZ twins.

In short, the strength of genetic factors can be estimated in two ways:

(i) How close is g_m to 1? It turns out that for most congenital malformations g_m is smaller than 0.3. In the previous cancer example, $c_m = 0$ because even for pair 1 there are different cancers,[24] thus $g_m = 0$.

(ii) How much is g_m larger than g_d? This can be expressed by the ratio: $g' = g_m/g_d$.

These conclusions are summarized in Table A.1a.

Inserting the values of c_m, d_m, c_d, d_d given in Yu et al. [18, Table 2] one gets the results shown in Table A.1b.

The estimates show that for all malformations the strength of genetic factors is far from 100%; in other words there is room for other factors than heredity, particularly for environmental factors and output dispersion. According to the g_m criterion, the strength of genetic factors rank as follows (from high to low): oral cleft, club foot, strabismus, spina bifida; according to the g' criterion the ranking is: club foot, oral cleft, strabismus (not defined for spina bifida).

In Table A.1b the fact that on average for the 4 malformations $g_m = 0.16 \pm 0.04$ which is well below 1 shows that genetic determination is rather weak. Thus, other factors may be at work.

[24] If one is only interested in whether there is cancer or not then $c_m = 1$ and $g_m = 1/5 = 0.2$.

Table A.1b
Estimates of the strength of genetic factors in malformation occurrences.
Source: The data are for 6,752 monozygotic twin pairs and 13,310 dizygotic twin pairs from the California twin program covering 1957–1982 [18].

Birth defect	p per 1000	MZ Concord. pairs c_m	MZ Discord. pairs d_m	MZ Ratio $g_m = \frac{c_m}{c_m + d_m}$	DZ Concord. pairs c_d	DZ Discord pairs d_d	DZ Ratio $g_d = \frac{c_d}{c_d + d_d}$	MZ/DZ $g' = g_m/g_d$
Oral cleft	2	2	7	22%	2	36	5.3%	4.1
Spina bifida	2	1	16	5.9%	0	33	0%	–
Club foot	4	5	17	22%	4	82	4.6%	4.8
Strabism	18	33	161	17%	27	412	6.5%	2.6
Average	6.5			16.7%			4.10%	3.83

Notes: The most significant results are in the g_m column for true twins. The fact that among such MZ pairs there are substantially more which are discordant than concordant (which translates in values of g_m notably lower than 1) shows a loose genetic determination. The results for g' are only significant for strabismus because for oral cleft and spina bifida the numbers of cases are somewhat too small.

Table A.1c
Estimates of the strength of genetic factors in cancer.
Source: The data are for 23,386 twin pairs from the "Swedish Twin Registry" covering the years 1959–1961 and 1970–1972 [48].

Type of cancer	MZ Concord. pairs c_m	MZ Discord. pairs d_m	MZ Ratio g_m (%)	DZ Concord. pairs c_d	DZ Discord pairs d_d	DZ Ratio g_d (%)	MZ/DZ $g' = g_m/g_d$
Specific cancers							
Lung	1	49	2.0%	3	112	2.6%	0.77
Stomach	2	74	4.9%	4	138	2.8%	0.93
Colon	8	153	2.6%	13	191	4.3%	1.16
Breast	22	257	7.9%	23	467	4.7%	1.68
Cervix	30	242	11.0%	27	412	5.1%	2.16
Prostate	19	137	12.2%	7	299	2.3%	5.30
Average			6.8%			3.6%	2.00
All cancers	182	1306	12.2%	257	2351	9.8%	1.23

Notes: The variables c_m, c_d, d_m, d_d, g' are defined in the text. "Concord" means "Concordant" (i.e. same disease in each twin of a pair); "Discord" means "Discordant". In the "Specific cancers" cases "concordant" means the same specific kind of cancer whereas in the "All cancers" row "concordant" means "any kind of cancer". The cancers are ranked by order of increasing values of g', that is to say increasing strength of genetic factors. The "All cancers" row includes more cases than the 6 types listed in the table.

A.4. Strength of genetic factors in cancer

So far, we have examined birth defects. Although it is at birth that these defects become visible, in fact they appear earlier during pregnancy. On the contrary, cancer appears late in the course of life. Therefore, one can expect important contributions of somatic mutations and environmental factors. It is for the purpose of comparison that we study this case.

Table A.1c gives estimates for the strength of genetic factors in cancer. Whether or not cancer can be seen as resulting from a congenital defect of the immune system is a matter of perspective. On average the estimates show that the genetic component is weaker than for the malformations given in Table A.1b.

When the concordance of monozygotic and dizygotic twin pairs are approximately of same value, i.e. $g' \sim 1$, it suggests a small influence of genetic factors. In such a situation one must check if this common value is higher than what would be expected on a purely random basis.

For all cancers except cervix and prostate cancer, on account of $g_m \simeq g_d$ there is little genetic influence. As the prevalence for all cancers is about $p = 6\%$ in the population over 15, Table A.1c shows that $g_m = 12.2\%$ is (slightly) higher than the random threshold of 6%. This suggests that family similarities may play a role, e.g. obesity, stress due to living or working conditions and so on.

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