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 “shut” the two others and to see whether or not there is 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 10%-20% in terms of coefficient of variation. As an example, the CV of the volume of E.coli bacteria immediately after binary fission is of the order of 10%.

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 dispersion effect. We conjecture that it will be particularly significant when major changes occur; this includes the early phase of embryogenesis or the 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 post-natal fall of infant mortality. For reasons which are not yet fully understood, this fall continues until the age of 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 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 and registers 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. Somehow, this feature should be visible on the infant mortality rate. How this conjecture can be tested is outlined in our conclusion.


Contents

Introduction: the “manufacturing dispersion” effect
Variability in biochemical reactions
From technical systems to living organisms: a physics perspective
Broad reach of congenital anomalies
Randomness of the dispersion effect
Rationale for an output dispersion effect
Control procedures
Why defect statistics give a biased picture
Are complex organs more affected by output dispersion?
The most frequent defects have close links with normality
Weak role of genetic factors in birth defects
Identification of output dispersion through phenotype variations
Outline of the paper

Fault-tolerant design
Tolerance issues in the industrial production of mechanical devices
The tolerance system as a way to mitigate the effects of manufacturing defects
Output dispersion in biological systems

Salient features of embryonic mortality
Implication of geometrical abnormalities for development of the embryo
Age-dependent embryonic mortality
General observations about embryonic mortality
Avian species. Fish species. Human fetal deaths
How can one explain that the death rate is highest at the beginning of embryogenesis?
A conjecture about embryogenesis in unicellular organisms
Influence of temperature on hatching rate

Salient features of the two phases of human mortality
Human infant mortality for all causes of death
The age of 10 seen as an equilibrium point between screening and wear-out
Infant mortality for specific causes of death

Conclusion
Main results
Rationale for cross species comparisons

Appendix A. Estimating the strength of genetic factors
Mutations and repair mechanisms
The twin methodology for assessing the strength of genetic factors
Strength of genetic factors in cancer
This paper is the first leg of an exploration in three parts; the two others are Bois et al. (2019a,b). Despite the connections the three papers can be read independently from each other.

Introduction: the “manufacturing dispersion” effect

In a characteristic way the abstract of a recent paper about birth defects begins with the following sentence: “The causes of birth defects are complex and include genetic and environmental factors and/or their interactions” (Chen et al. 2018). In other words, genetic and environmental factors are seen as the only sources of birth defects. 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.

Variability in biochemical reactions

Thousands 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 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 volatility 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 (Wallden et al. 2016, 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 $CV \approx 10\%, 20\%$ re-

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1In 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 controled laboratory experiments.
spectively. Actually, variability at cell level has already been recognized and studied (at least qualitatively) in the 1910s and 1920s as will be documented later on.

**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 it is tried by physicists and biologists who share a similar turn of mind.

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 pretty well as starting points for the investigation of phenomena that remain mysterious.

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 functions 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.

**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 observed 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.
lies 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** The behavior of living organisms is to a large extent genetically controled. As an example 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.

(i) 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 5cm deep by scratching the ground. (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. A delay of up to 6 days will make little difference in hatching time. 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 on the outside of the nest into the middle and the middle ones out so all are evenly warmed. A graph presented in the section on embryogenesis shows that in terms of temperature there are very strict 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 one, two or three times a day (each time for about 15 minutes) to find food and water and to defecate. Nonetheless, a hen will usually lose weight while brooding. (viii) *Last three days.* Toward the end of the incubation and particularly 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 close to or 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. In natural conditions the hen will show her chicks how to identify and peck food.

It is by purpose that we have described this process in some detail to show how eas-

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4Injections of the hormones prolactin, luteinizing, and oestradiol to non-broody hens induces broodiness.
ily it can be disrupted or become sub-optimal (in the sense of a reduced hatching rate). Usually the disruptions which may trigger anomalies remain hidden to the outside observer. On the contrary, in the brooding process inappropriate environmental conditions which at each step may derail the process occur in full view and can be identified. This gives an intuitive view of the notion of manufacturing volatility. Just as for phenotype characteristics, there is also a substantial variability in brooding ability and behavior. Some hens are very good at brooding while others are not. For instance, first time brooders might not stay broody for very long.

In the same way as birth defects are nothing but amplified forms of normal variability, similarly some forms of behavior become sufficiently extreme to be labelled as “abnormal”. Here are a few examples.

- Sometimes, hens will go broody without eggs underneath them. In some cases they may continue to sit on empty nests for 2 or 3 months.
- In many bird species males and females alternate sitting on the eggs. Curiously, the same behavior was observed for two hens (Buibaku et al. 2010). During the day they were alternating: one was incubating from morning till noon while the other was out to eat, drink, dust bath and rest. Roles were interchanged around midday. During the night the two hens were jointly brooding. However, the result was not satisfactory in the sense that of the 22 eggs they were brooding only one was able to hatch.

**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 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 will also make a difference.

**Rationale for an output dispersion effect**

There are several motivations for introducing the dispersion effect.

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5In other words, the analysis of the brooding process offers an excellent observational opportunity to explore the interaction between genotype and environmental conditions. To our best knowledge, this field of research has not yet been explored in a systematic way.

6A simple test consists in putting an egg in front of a hen. If she pulls the egg under her she may be well “gifted”.

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

8In 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.
(1) **Most birth defects are unexplained.** For most birth defects the factor responsible is not known. A recent publication in the “British Medical Journal” (Feldcamp et al. 2017) tells us that in a total of 5,504 birth defects in 270,878 children born in the state of Utah in 2005–2009, the etiology is unknown for 3,390 which represents 80% of the cases. Of the 1,104 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 (e.g. Ahmed et al. 2017) 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 A, 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 as 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 Ruth Stocking (1913,1915), Ralph Middleton (1915), Herbert Jennings (1916), Bessie Noyes (1922). Uniparental reproduction (also called asexual reproduction) occurs in two cases.

The simplest is the reproduction by fission of unicellular organisms. In her thesis (Noyes 1923) 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. metazoa) 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 (Noyes 1923).

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 (Drummond...
(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 is simply the fact in any manufacturing process there are two parts: (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.

In real life, a design is never carried out with absolute accuracy. If a table is designed with a width of 3m, in reality its width will be comprised between $W_1 = 2,999\text{mm}$ and $W_2 = 3,001\text{mm}$. 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 3m, then the $W_1$ table will get 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 (Tomasetti et al. 2015). This discovery provided a natural explanation for the fact, known since the 1920s (Greenough 1925, Patey et al. 1928), 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 organs in the earliest stage of their development are most sensitive to teratogenic (i.e. causing developmental malformations) factors at the time of their appearance. This point is shown very clearly in a paper by Uchida et al. (2018); 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

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9To use for living organisms the expression “manufacturing process” may seem odd. However, our objective is precisely to watch living systems from the perspective of technical reliability science.
than) the mechanism identified in Tomasetti et al. (2015) 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 below) 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
Table 1: Incidence of birth defects in high accuracy processes.

| Birth defect                  | Description            | Prevalence (per 1,000) |
|-------------------------------|------------------------|------------------------|
| “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 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%).

Source: Child health, USA 2014, Table 1: National prevalence estimates of selected major birth defects; Gunton et al. (2015); for spina bifida occulta: estimate of the “National Institute of Neurological Disorders and Stroke”.

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.

**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 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.

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.

**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. (Vyas 2016). 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 polydactily (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.

**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, 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.

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.

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 blueprint 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% (Schaeffer et al. 2007).

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.

Weak role of genetic factors in birth defects
At first sight it may seem that the dispersion effect is only of marginal importance

11It 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.
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 (1965, p.166). In a study of family characteristics of congenital malformations done 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 6,752 monozygotic (MZ) twins and 13,310 dizygotic (DZ) twins in California observed from 1957 to 1982 (Yu et al. 2019).

MZ twins share 100% of their genome whereas DZ twins share on average 50% of their genome (Yu et al. 2019, p.18). In Appendix A we explain a method for assessing the role of genetic factors. When applied to the data given in Yu et al. (2019) it leads (see Appendix A) 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\footnote{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.} is significantly associated with congenital defects (Yu et al. 2019). However, why should smoking of the mother affect one twin and not the other?

**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.

![Illustrations](image)

**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 \( m = 455 \text{ mg} \) and standard deviation \( \sigma = 70 \text{ mg} \) which gives a coefficient of variation \( CV = 17.0\% \). For all nineteen pure lines totaling 5,494 beans \( CV = 19.9\% \). These experiments were done by Wilhelm Johannsen in 1900-1902. **Bottom:** Dispersion in the aspect of *Diffugia 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 latter 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\%. **Sources:** Johannsen 1903 (p.22-28), Jennings 1916 (p.438-439).

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 which is an integer smaller than 17.

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

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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.
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.

Table 2: Mechanisms related to congenital anomalies.

| Mechanism                        | Passed to offspring | Identification test               | Example            |
|----------------------------------|---------------------|-----------------------------------|--------------------|
| Design glitch                    |                     |                                   |                    |
| 1 Mutation in DNA of gem cells   | Yes                 | Genome sequencing                 | Trisomy 21        |
| 2 Mutation in DNA of somatic cells| No                  | Non inheritable abnormal cells    | Cancer             |
| Manufacturing glitch             |                     |                                   |                    |
| 3 Environmental interference     | No                  | Epidemiological studies           | Effect of nicotine |
| 4 Random output dispersion       | No                  | Uniparental reproduction          | Strabism           |
| Repair mechanism                 |                     |                                   |                    |
| 5 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.

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 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

\[14\] This statement just results from basic probability theory. Peto’s paradox relies on what happens not at cell level but at the level of the organism (“Why don’t all whales have cancer?”). A mutated cell will lead to cancer only if it is not removed by the immune system. Is the immune system of the mice used in laboratories not affected by the fact that they are pure line mice?
possible environmental factors. Thus, for beans one can mention the position of the beans in the pods and the location of the pods on the plant. However, why should such discontinuous factors lead to almost perfect Gaussian distributions? 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).

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 (1915).

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.

**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.

**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 (Dubrova 2013). 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, namely: “Synthesis of reliable organisms from unreliable components” (Von Neumann 1956).

**Tolerance issues in the industrial 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 10mm 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 10.003mm and 9.996mm 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 10.000mm. This will be possible for hole 1 but not for hole 2. In short, even small discrepancies may prevent assemblage.

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 fourk) 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.

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 10mm).

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. ±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.

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 in 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
Fig. 2 Within and out of tolerance areas when a process depends 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 (note that it may have another shape than a simple disk). (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.

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” (Drummond et al. 2009). 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 (Depree et al. 2001). 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 which prevents 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).

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.

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.

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 20mn 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 1mm. 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. (2004, 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. (2004, p.222)*

**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. (2017).
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 1,000 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.

Sources of the data: Chicken (broiler): Peñuela et al. (2018, p.6505), number of fertilized eggs ($n$) = 3,146; turkey: Fairchild et al. (2002, p. 262), $n = 51,764$; European perch: Alix (2016, p. 161), $n = 13,500$; humans: French et al. (1962, p.840,844), $n = 3,083$.

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. 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 1,000 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.

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 (Romanoff 1949).

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 (Hutt 1929). 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. If, for some reason, the eggshell is too hard or too thick the chick may be unable to break it.

Fish species

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16This is in spite of the fact that the experiment involved 3,240 eggs and that 471 of these embryos died. As the turkey experiment involved 10 times more eggs its results are more reliable.

17For 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.
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.

**Human fetal deaths**

The study described in French et al. (1962) took place in the island of Kauai in the state of Hawaii. During the four years of the study there were 3,083 pregnancies, 273 fetal deaths and 2,777 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.

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.

**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 embryogene-
sis. 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 hours during the first 24 hours.

**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 hours before division actually occurs (Laub et al. 2000, p.2145). This phase (which consists of successive so-called G₁, S and G₂ 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 (Cryms et al. 1999) 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.

**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—5 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.

**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.

**Human infant mortality for all causes of death**

As our starting point we consider infant death rate curves for humans as shown in Fig. 2a, b\(^\text{18}\).

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 the readers on two aspects. (i) Fig. 4a shows that the death rates exhibit little fluctuations. (ii) Fig. 4c shows that the 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

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\(^{18}\)More details about infant mortality can be found in Berrut et al. 2016.
several countries shows that these curves remain much the same in all developed
countries. As an illustration, one can look at the death rate curves for the UK shown
in Berrut et al. (2016)

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 demon-
strated by the fact that weekly or monthly death rate curves show fairly large fluc-
tuations. This suggests that evolution as a function of age is much more stable than
changes in the course of (calendar) time. As a matter of fact, it will be seen in Bois et
al. (2019a) that this stability is greater for young-age deaths than for old-age deaths.

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 \( \gamma \) of the order of 1. 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 \( x_0=\text{number of live births} \),
\( \Delta x=\text{number of deaths in the age interval } \Delta t \); 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 \( \mu \), the denominator \( x_0 \) is replaced by
the number \( x(t) \) of individuals alive at the beginning of the age interval \( \Delta t \). 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). Sources: 1923 (a) Under
one year: Linder et al. 1947 p.574, (b) Over one year: Linder et al. 1947, p.150 (gives in fact 1920); 1960 (a)
Under one year: Grove et al. 1968, p.210-211, (b) Over one year: Grove et al. 1968, p.318.
Now we describe the three salient features of the shape of the infant death rate curves.

(1) 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) 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 3,600 days that is to say about 10 years. If one considers that the maximum life span is about \(T_{\text{max}} = 100\) years this corresponds to 10% of \(T_{\text{max}}\). After the age of 10 years the death rate increases steadily and exponentially up to \(T_{\text{max}}\) 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) 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 \(\gamma\) is of the order of 1.

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.

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). Fig 4b, Fig. 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

\[^{19}\text{By this expression we mean that a fall from 1,000 to 100 will take place between day 1.5 and 7, whereas from 10 to 1 it will take from day 150 to day 700 (approximately).}\]

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

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

This makes the two functions really different in nature. For instance, the exponential form of Gompertz’s law absolutely
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.

**Conclusion**

**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 1,000) 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 of 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.

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 (Bois et al. 2019b) we propose two simple physical models which provide a clearer insight than in vivo biological organisms.

**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 newborn.

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 0.2mm in length and 0.03mm 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, $\Delta c$, is the same, the skin thickness, $\Delta x$, 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 (Bois et al. 2019a).

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.

### Appendix A. 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” (Kolata 2006), demographic and epidemiological research shows that for most human characteristics (e.g. lifespan or diseases) there is only a very 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 like the study by Ahmed et al. (2017) 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 some aspects of harmful mutations leading to anomalies.

**Mutations and repair mechanisms**

In a living organism harmful mutations can occur at three levels. (i) Germ cells. (ii) Stem cells, i.e. cells no 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. 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. If there are repair mechanisms it means that the static picture with a rigid connection between defective genes and abnormalities must be replaced by a dynamic vision.

**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 et al. (1981) and Tishler et al. (2007). 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 (Hladíková et al. 2013).

- 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)

The authors conclude that “environmental factors play an important role in breast cancer development”. Instead of mysterious “environmental factors” such outcomes can also result from a random dispersion of manufacturing outputs.

Next, we consider this problem in a more general way.

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

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22There 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.
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 1,000 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,

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

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, thus $g_m = 0$.

(ii) How much is $g_m$ larger than $g_d$? This can be expressed by the ratio: $g' = g_m / g_d$. In the cancer example: $g' = 0$.

These conclusions are summarized in Table A1a.

Inserting the values of $c_m, d_m, c_d, d_d$ given in Yu et al (2019, Table 2) one gets the results shown in Table A1b.

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,

\[23\] If one is only interested in whether there is cancer or not then $c_m = 1$ and $g_m = 1/5 = 0.2$. 


Table A1a: Twin variables for estimating the strength of genetic factors in malformation occurrences.

|                | MZ Concord. pairs | MZ Discord. pairs | MZ Ratio | DZ Concord. pairs | DZ Discord. pairs | DZ Ratio | MZ/DZ |
|----------------|-------------------|-------------------|----------|-------------------|-------------------|----------|-------|
| 100% genetic   | \(c_m\)           | \(d_m\)           | \(g_m\)  | \(c_d\)           | \(d_d\)           | \(g_d\)  | \(g' = g_m/g_d\) |
| 0% genetic     | \(Np^2\)          | \(Np\)            | \(g_m = p\) | \(Np^2\)          | \(Np\)            | \(g_d = p\) | \(g' \approx 1\) |

Notes: \(N\) is the population of the sample. MZ means monozygotic (true twins) and it corresponds to the index \(m\). DZ means dizygotic and it corresponds to the index \(d\). “Concord.” means “Concordant” (corresponds to the variable \(c\)). “Discord.” means “Discordant” (corresponds to the variable \(d\)). 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.

Table A1b: Estimates of the strength of genetic factors in malformation occurrences.

| Birth defect   | \(p\) per 1,000 | MZ Concord. pairs | MZ Discord. pairs | MZ Ratio | DZ Concord. pairs | DZ Discord. pairs | DZ Ratio | MZ/DZ |
|----------------|-----------------|-------------------|-------------------|----------|-------------------|-------------------|----------|-------|
| 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: Although for oral cleft and spina bifida the numbers of cases are somewhat too small the fact that among MZ pairs there are much more discordant pairs than concordant pairs (which translates in a value of \(g_m\) much lower than 1) shows a loose genetic determination. The results for \(g'\) are only significant for strabismus; for the other defects there are too few DZ cases.

Sources: The data are for 6,752 monozygotic twin pairs and 13,310 dizygotic twin pairs from the California twin program covering 1957–1982 (Yu et al. 2019).

strabismus, spina bifida; according to the \(g'\) criterion the ranking is: club foot, oral cleft, strabismus (not defined for spina bifida).

In Table A1b we see that: (i) \(g_m > p\), (ii) \(g_d < g_m\) and (iii) \(g' > 1\) which suggests that genetic factors play a role in the malformations. However, the fact that on average for the 4 malformations \(g_m = 0.16 \pm 0.04\) which is well below 1 show that genetic
determination is rather weak. In other words, other factors may be at work.

**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 A1c: Estimates of the strength of genetic factors in cancer.**

| Type of cancer | MZ Concord. pairs | MZ Discord. pairs | MZ Ratio | DZ Concord. pairs | DZ Discord. pairs | DZ Ratio | MZ/DZ |
|----------------|-------------------|-------------------|----------|-------------------|-------------------|----------|-------|
| MZ MZ MZ DZ DZ | cm, dm, g_m (%)    | cm, dm, g_d (%)    | g_m/g_d  | cm, dm, g_m (%)    | cm, dm, g_d (%)    | 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              | 3.6%     | 1.23  |

Notes: The variables cm, cd, dm, dd, 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.

Sources: The data are for 23,386 twin pairs from the “Swedish Twin Registry” covering the years 1959–1961 and 1970–1972 (Ahlbom et al. 1997).

Table A1c 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 A1b.

When the concordance of monozygotic and dizygotic twin pairs are approximately of same value, i.e. g′ ∼ 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 ≈ g_d there is little genetic influence. As the prevalence for all cancers is about p = 6% in the
population over 15, Table A1c 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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