Evolocus

Article

Nomogenesis and the logic of chance

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Evolution of available genomes was shown to be proceeding through random changes, the changes that comprise the main modus of evolution (Koonin, 2011)[1]. Morphological evolution of available and extinct *Metazoa* was shown to be going on the basis of law, by means of precession of characters, where characters originally manifested in the young along in the course of time and evolution were displayed also in adult descendants (or supposed descendants) of that organism (Berg, 1922)[2]. This contradiction is obviously solved in nature, where the appearance of any new genetic locus in the genome and its further expression in the phenotype can be separated by unlimited period of time and by unlimited number of generations. The management of dormant genetic loci has come from the previous evolutionary stage, unimaginable today, where organisms were open systems with respect to the flow of genetic elements and were collecting, discriminating and storing genetic elements from the external environment. This was an important period when multiple systems for blocking and unblocking of genetic loci came into being. However even before this stage, it was even more fantastic evolutionary period where replication, transcription and translation were absent and Eigen cycle was not possible, but organisms were collecting randomly available components (proteins, RNA and DNA) by means of action acceptors (Anokhin, 1955)[3,4] – sites of double-stranded DNA mechanically compatible with useful components. Action acceptors themselves were unable to be replicated by modern way (no DNA polymerase!), but they were collecting their pseudo-copies from the environment – the pieces of DNA that were born in the environment and occurred to be compatible by chance with current action acceptors. Action acceptors, – the structures that sense presumably useful results or substances, were directing evolution from the early beginning and they are directing it today through activation and deactivation of dormant genetic loci.

In animals like mice, rats and guinea pigs, and also in humans (holocaust survivors and their progeny)[5], the phenomenon of phenotypic inversion can be observed[6-15]. Phenotypic inversion is defined as the opposite quantitative changes in untreated offspring with respect to treated, *e.g.* drug-treated, parents[11]. Phenotypic inversion was also reported in plants[16] and insects[17]. The term was introduced in 2004[18] and it is in use in connection with transgenerational epigenetic compensation[10-15,19-21].

In humans[5] and guinea pigs[15] the phenomenon of phenotypic inversion was registered also in methylation of DNA. Thus, the demethylation of 5-methylcytosine behaves here as a phenotypic trait and not as a heritable basis of transgenerational effects. Very often phenotypic inversion was obtained as a result of paternal drug treatment (prenatal, neonatal and adolescent), using such drugs as morphine[8-14], thyroxine[6,7,10-14] or complex substances like plastic mixtures[22]. However less often it was reported that phenotypic inversion can be expressed during lifespan of a given descendant in a semi-stochastic "all-or-none" fashion[14] (as "unstable, destabilized"[23]).

An example of such "all-or-nothing" expression of phenotypic inversion is shown in the **Fig. 1**, where randomly enhanced water consumption is recorded in female guinea pig, obtained from

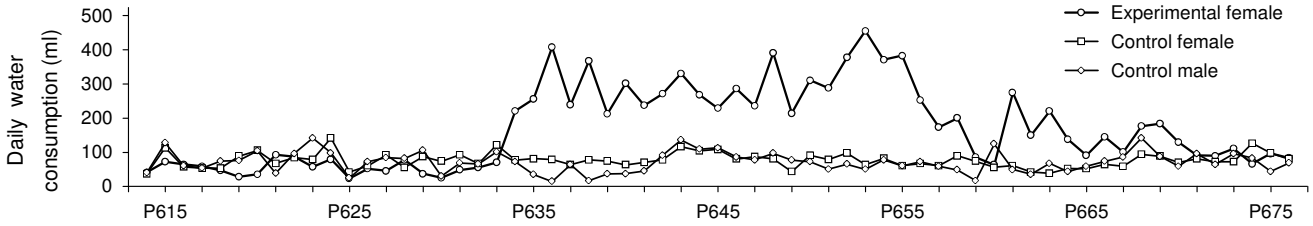

Figure 1 | Randomly expressed increased water consumption in the experimental female guinea pig, obtained from female with low adult water consumption and normal male. Postnatal days P614-P676 are shown. The stochastically increased water consumption in this female is in contradiction with the phenotype of her mother. Her mother was born in a litter of four, among normal littermates. The mother had decreased water consumption and increased locomotor activity and curiosity in home cage, observed during childhood, adolescence, adult life, and during pregnancy and lactation also.

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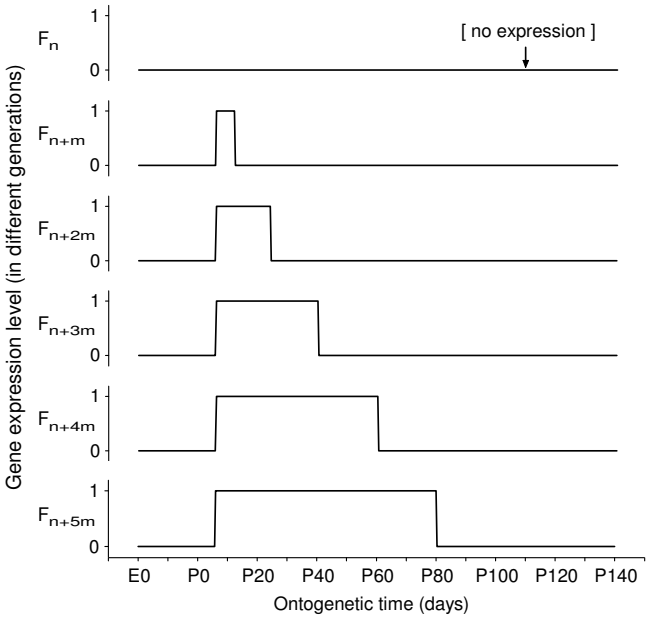

Figure 2 | Expression of one previously dormant genetic locus. Leo S. Berg has described the "precession of characters" in 1922: "… latent characters (factors, *genes*) originally manifested in the young alone… in the course of time and evolution are displayed also in the adult descendants (or supposed descendants) of that organism" [p. 75[2]; the word "*genes*" was italicized by Berg]. Ontogenetic time scale is shown for such animals as rats, keeping in mind experiments with methadone and morphine (Figs. 1[24] and 2[24], Supplementary Fig. 5a[11]). E0 – the first embryonic day, P0 – the first postnatal day.

female with unusually low water consumption. Note the random character of the expression of this phenotypic inversion (see also **Supplementary Figs. 2-3**). Of course, phenotypic inversion is supposed to be a result of compensatory changes[11]. Phenotypic inversion was also registered as an enhanced sensitivity to morphine in the F_2 progeny of chronically morphine-treated male Wistar rats, shown in the **Supplementary Figs. 4-7**. The relative lack of such observations in literature is a consequence of the absence of long-term records (it is thought to be difficult or impractical to monitor all descendants during their lifespan). Such records do exist for daily water consumption in guinea pigs (500 days) and morphine analgesia in rats (25 time points distributed among 7 days). Where long-term records are available, random "all-or-nothing" expression of phenotypic inversion during lifespan of a single animal is usually obvious.

Leo S. Berg has shown that new morphological changes can appear in evolution on the basis of law – by means of the precession of characters (**Fig. 2**). The time scale of shown example is given for the disturbance of opiate system in rats. This relatively new example was not discussed by Berg. The appearance of any new morphological trait, described by Berg, is an "all-or-nothing" response that is non-controllable or poorly controllable in amplitude, but nicely regular in temporal dimension during both ontogenesis and phylogenesis.

In modern experiments with transgenic mice, schematically shown in the **Fig. 3**, the disappearance or attenuation of phenotype in successive generations was observed rather often, but it was not reported so often due to social pseudo-scientific reasons. Both the observations of Berg concerning the appearance of dormant traits in evolution and the modern observations concerning the disappearance of phenotype in successive generations of transgenic mice demonstrate that *Metazoa* have sufficient molecular tools to control dormant genetic loci and to use them purposively.

The evolution of biochemical syntheses, described by Norman H. Horowitz (1945)[25] (**Fig. 4**), implies that any chain of biochemical reactions was developing in evolution from its final result (product). And all further steps were growing from the right to the left (shown as sequence: ד ← ג ← ב ← א), where each new enzyme was introduced by purpose – to provide substrate for previously existing process. Thus, this chain as a whole was build up as a purposive structure, being strictly purposive during each step of its evolution. Each additional step was satisfying the pre-existing action acceptor – the structure that can sense the presence and can use the result of this newly added step. The whole schema of Horowitz is an example of evolution, determined by law, determined by the requirements of pre-existing functional systems.

The law of homologous series in variation, discovered by Nikolai I. Vavilov (1922)[26], also can be used as an illustration of evolution, determined by law. Usually, similar heritable deviations (variations) in different species are explained by mutations in similar important genes that are normally expressed. But if it would be so, such events would be very rare, because such changes would be recessive and observable only in homozygous samples. Contrary to this, similar variations are formed by suddenly expressed dormant genetic loci those are also similar between species. Their sudden expression produces detectable effect in heterozygous individuals, being obviously dominant. Here we would like to repeat that in the experiments with paternal drug treatment[6-14] mothers were always drug-naïve.

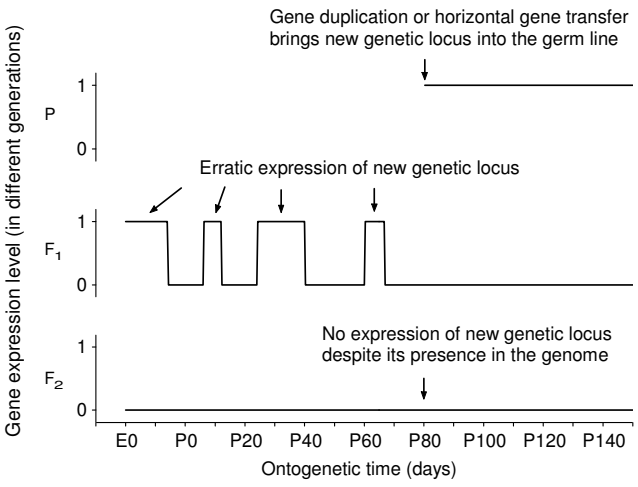

Figure 3 | New genetic locus is submerging into dormancy. In mammals, this process needs at least three shown generations (theoretically, in an idealized situation). In real life, 6-12 generations are required to bring new genetic locus into completely dormant state (many experiments with transgenic animals, mainly mice, are pointing out that this estimation is correct, at least for some genetic loci)[27,28]. Similar results, being frequently obtained, remain typically unpublished (nobody would like to report the disappearance of the phenotype discussed in the previous own article).

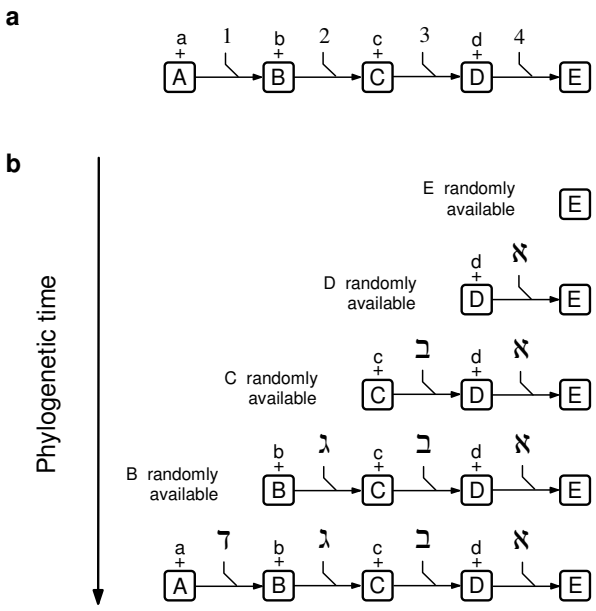

Figure 4 | The evolution of biochemical syntheses by Norman H. Horowitz (1945)[25]. **a**, Chain of biochemical reactions, shown schematically from substrate A to product E, is catalyzed by a set of specific enzymes 1, 2, 3, 4. **b**, In evolution, the order of appearance of specific enzymes is the opposite to the mentioned above and it can be shown as א, ב, ג, ד. Substance, known now as a product, at some point of evolution was randomly available from the environment. At the moment of its partial disappearance from the environment, but under condition that it still could be produced somehow from other available substances, its synthesis was beneficial and specific enzyme came into being.

So, we are dealing with dominant effects in the progeny – with expression of previously dormant genetic loci. Similar results (*i.e.* expression of previously dormant genetic loci) were obtained during domestication of silver foxes by Dmitry K. Belyaev[29,30]. Historically, homologous series of variation were first observed in wheat, which is usually self-fertilized, and later the same regularities were confirmed in rye, a typical cross-fertilized plant (p. 58)[26].

The term "action acceptor" was first introduced by Peter K. Anokhin in 1955[3,4] to describe behaviour of animals, at that time – dogs, as a brain-related feature. However the first action acceptors were present even before the appearance of replication, transcription and translation. Strictly speaking, the action acceptor is the first structure that appears in phylogenetic development of any functional system and this structure can sense and potentially use randomly appearing results, those are born in the external or internal environment by chance. All processes, even so complex as cell division, were appearing in evolution as random events. First – appearing purely by chance. Then – appearing with increased probability during some periods and appearing with decreased probability during some other periods of ontogenesis. Finally – appearing as clearly deterministic and well-controlled processes. Each time the action acceptor was formed before the next evolutionary step, and the next evolutionary step, like the next ferment in a biochemical chain, was found and raised up by the pre-existing action acceptor.

Typically our attention is focused upon the effector parts or production lines that produce "real result". If we see some feedback loop, we have a tendency to accept it as a relatively late addition that just slightly improves this system. However in real life, all feedbacks with their action acceptors were formed in evolution before all currently observable effector parts of given functional systems. It was an action acceptor that was the main acting agent in organization of all effector components from randomly available parts. Each of these parts could be first introduced at any previous evolutionary stage by chance.

Thus, from the early beginning the evolution was proceeding under control of very short and very strong feedback loops – internal feedback loops from the action acceptors. The shortest feedback loop was typically the strongest one. This type of evolution looks teleological and internally purposive. It is teleological and internally purposive – no secret here. For discussion of real teleology and pseudo-teleology of Darwinism we would like to refer to the book of Nikolai Ya. Danilevski,

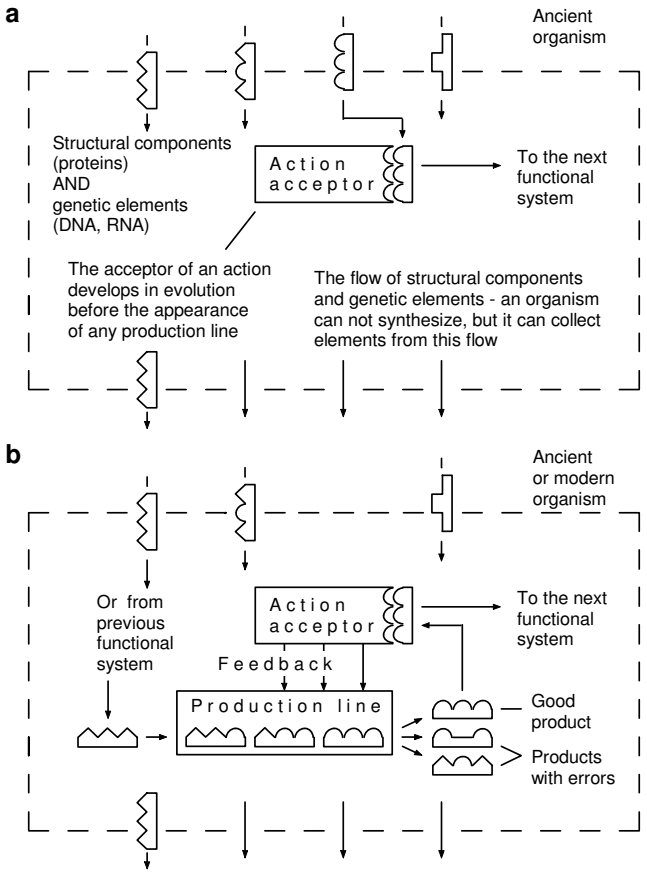

Figure 5 | Action acceptor in evolution. **a**, Early (ancient) organism was an open system not only in terms of energy, but in terms of its structural and genetic components also. It was not able to synthesize, but it was able to collect many components from the environment. The process of collection of components was performed by a set of action acceptors. **b**, Evolution of any production line starts from the acceptor of an action – from formation of potential feedback loop which appears in evolution before the first effector components of given functional system. Functional system is an entity that is searching for or is supporting the existence of some positive (useful) result with a help of feedback loop. The detector of useful result (action acceptor) is the first element in formation of feedback loop, see Fig. 6.11 (p. 241)[4] and Fig. 6.18 (p. 253)[4].

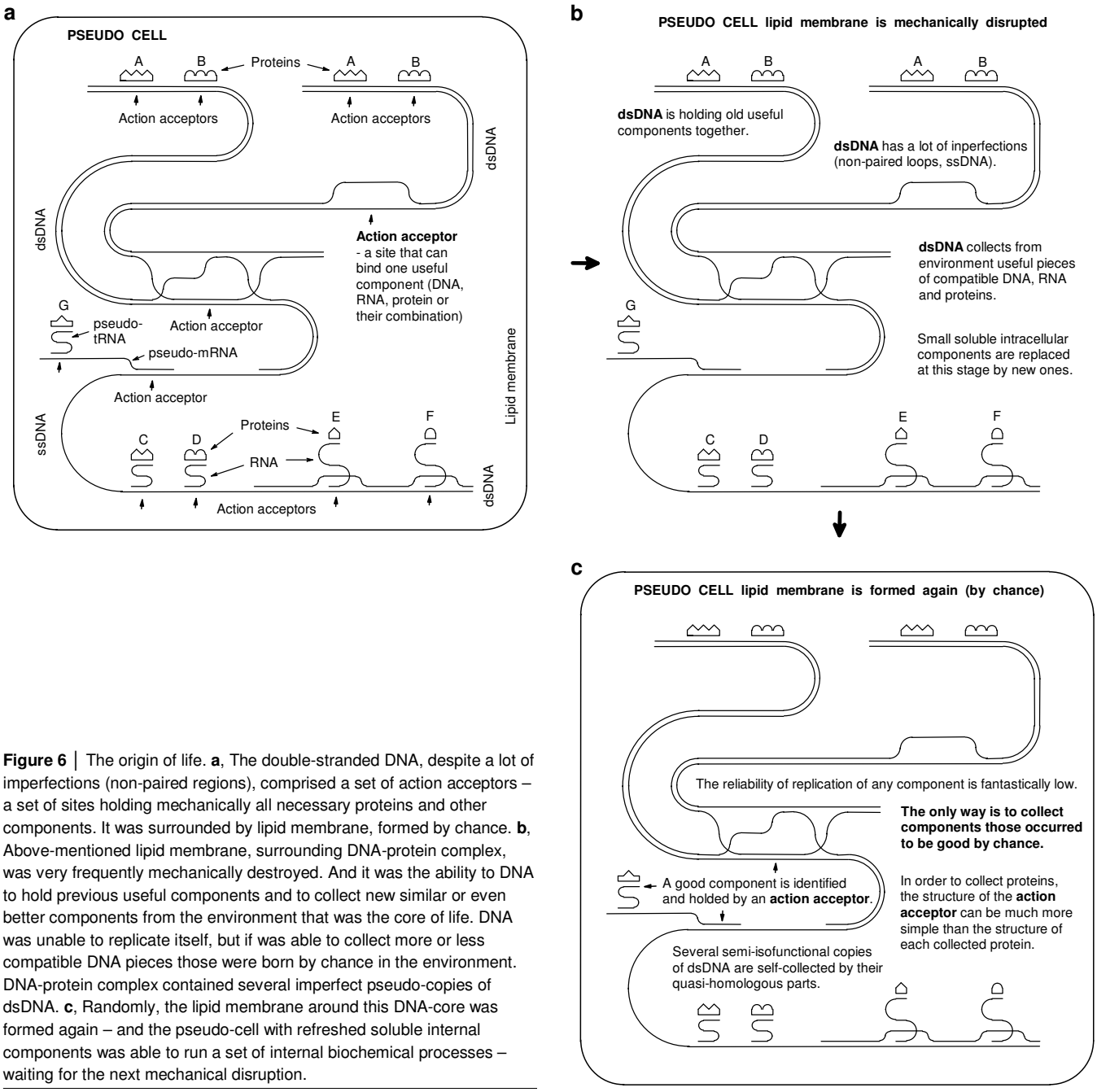

Figure 6 | The origin of life. **a**, The double-stranded DNA, despite a lot of imperfections (non-paired regions), comprised a set of action acceptors – a set of sites holding mechanically all necessary proteins and other components. It was surrounded by lipid membrane, formed by chance. **b**, Above-mentioned lipid membrane, surrounding DNA-protein complex, was very frequently mechanically destroyed. And it was the ability to DNA to hold previous useful components and to collect new similar or even better components from the environment that was the core of life. DNA was unable to replicate itself, but if was able to collect more or less compatible DNA pieces those were born by chance in the environment. DNA-protein complex contained several imperfect pseudo-copies of dsDNA. **c**, Randomly, the lipid membrane around this DNA-core was formed again – and the pseudo-cell with refreshed soluble internal components was able to run a set of internal biochemical processes – waiting for the next mechanical disruption.

published first in 1885[31-33], – it is fantastically important even today. As soon as functional system occurred to be equipped with even weak internal feedback loop – it has information about its own efficiency. And "efficiency" was determined in physiology by Alexander M. Ugolev[34,35] as relation of positive effects to negative ones ("cost factors"). It might be difficult to imagine "ideal organism", but we can always imagine "ideal functional system" – a system that is absent, but its positive result is achieved – this idea was first introduced by Genrich S. Altshuller[36] with respect to technical systems. The increase in complexity, observable in evolution, is not a purpose *per se*, but higher complexity is often, but not always, linked with higher efficiency. Parasitic organisms, evolving towards simplicity, are also good examples of the principle of efficiency.

Thus, any functional system of the organism has an ability, at least theoretically, to evolve towards "ideal functional system" and it can do so using its own internal feedback loops. It would be an error to assume that such feedback loops are good only for relatively simple optimization of the process. Any process exists usually under the pressure of contradictive forces and requirements. An attempt to increase one positive feature typically leads to decrease of another positive feature or to increase of some cost factor. Only the invention that can increase the main positive effect without the increase of the main cost factor would be really important evolutionary step, and this step will be done also with participation of local feedback loops, but the last remark does not mean that this step will be easy to perform.

As shown in the **Fig. 5**, the formation of an action acceptor and the formation of potential feedback loop are preceding in evolution the appearance of effector components of given functional system. The structure that senses the positive result develops in evolution first of all. At the beginning the result can be achieved only randomly – due to pure chance. The effector components will increase the probability of the appearance of positive result only later in evolution.

In modern organism, randomly available genetic and structural components are recruited by the action acceptor into production line in order to achieve qualitatively and quantitatively acceptable final result of this functional system. In modern organisms some action acceptors can be fantastically complex, distributed among multiple cells, but their main function remains the same – to search for and to support the desirable state of the organism or situation (not just to sense more or less good products among products with multiple errors). With respect to genetic components it was necessary not only to collect them, but to put them into domesticated state. The domesticated state means that the organism has an ability to switch given genetic element "on" and "off". The "on-off" switch – presumably reversible genetic change – has appeared in evolution even before the appearance of reliable replication. It means that an ancient organism was unable to reproduce incoming genetic elements, but it was able to switch them "on" and "off" in accordance with requirements of this organism.

As shown in the **Fig. 6**, the life on Earth has started when reliable replication, transcription and translation were absent (everything – below Eigen threshold[1,37]). Trans-membrane transport and trans-membrane potential were absent also. However, double-stranded DNA comprised the core of life. Its task was to collect and hold together all other necessary components (more or less similar DNA, more or less useful proteins and more or less useful RNA – all of them were randomly available from environment – they were developed by pure chance at the beginning of life). RNA was served as an intermediate factor in order to hold useful proteins that were not interacting with dsDNA sufficiently.

The mechanical disruption of this pseudo-cell was not only an analogue of cell division, but it was also an analogue of cell feeding. Whether the above-mentioned collection by dsDNA of more or less similar pieces of dsDNA together with other components could be described as "compositional inheritance as a mechanism of self-reproduction"[38] is an open question. At the beginning of life the mechanical disruption of pseudo-cell was really chance event. Only afterwards the pseudo-cell was able to increase probability of mechanical disruption at some stage of its existence and to decrease probability of mechanical disruption at some other stage of its existence.

Note that proteins that were binding to dsDNA directly, at the next stages of evolution will be "transcriptional factors". Replication, transcription and translation were developed under the control of action acceptors that were collecting only more or less successfully replicated, more or less successfully transcribed and more or less successfully translated components. Action acceptors were (and they remain!) the core elements of life that were able to compensate the fantastically low reliability of replication, the fantastically low reliability of transcription and the fantastically low reliability of translation. All three above-mentioned processes were developed under the control of very

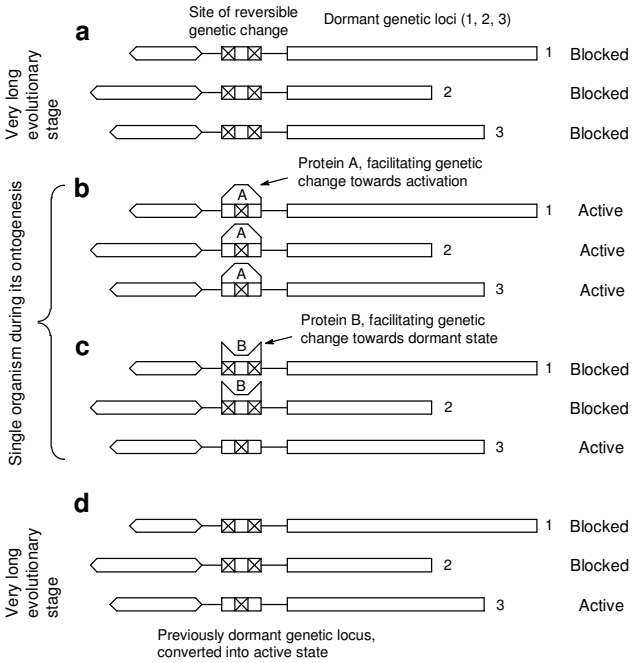

Figure 7 | Activation of previously dormant genetic locus in evolution. **a**, Three dormant genetic loci, each with reversible genetic change in the area of regulatory sites, are shown. **b**, In a deeply stressful situation the specific protein A is expressed, it binds to the site of reversible genetic change and increases the probability of its conversion into active state. **c**, In the exactly the same organism the protein B is expressed, it binds to the same site of reversible genetic change and increases the probability of its conversion into dormant state, but it can not do so with very highly expressed gene # 3. **d**, All previously expressed proteins A and B are finally disappeared, but previously dormant gene # 3 remains in active state (accessible for further regulation of its expression) forever. Similar process was called "orthoselection" in 1934 by J.W. Harms (Harms discussed the transition of vertebrate animals from water to land through multiple attempts, linked with transition of genes from "active" into "passive" state and *vice versa*)[39,40]. See **Supplementary Information**.

local, very short and very strong feedback loops. All proteins, facilitating necessary reactions, were collected together with products of the above-mentioned reactions by dsDNA, even despite any "knowledge" of their interactions were absent in the system (useful components should be held together – that is the principle). Very complex machinery of replication, transcription and translation was formed by means of collection of components that were formed independently and purely by chance. It means that DNA templates and proteins that were later formed of the basis of these templates, at the beginning of life were collected together just because the presence of templates is correlated with the appearance of above-mentioned proteins – both templates and proteins were formed at the beginning of life independently and mainly by chance.

As a short summary we can say that the evolution of the genome of any organism is always random – it is directed only by chance (Koonin, 2011)[1]. Morphological evolution and physiological evolution in general is always determined by law (Berg, 1922)[2]. And it was so even before the appearance of replication, transcription and translation. We can suppose that the very first action acceptors have appeared in evolution also by chance. As soon as the first action acceptors were present and

were able to collect from the environment useful components of different nature, randomly available (DNA, RNA, proteins), the first functional systems were formed and all further evolution was dictated by the requirements of the pre-existing functional systems. This process was and it is internally purposive, however some final goal is not absolutely necessary for its existence. It is sufficient to have local vector of development, each time based on local efficiency of currently present functional systems. This vector sometimes can be erroneous and it can lead to the extinction of the species, but it is always present (just because functional systems with their feedback loops are always present inside given organism).

Thus, evolution is a purposive process, and each its step is based on local efficiency. These are no analytical means that could distinguish between the results of the above-mentioned process and the results of evolution, directed by God, if our understanding of God is provided by Orthodox Judaism. In both cases all local decisions are solutions of contradictions between local positive effects and local cost factors. Thus, both descriptions have equal relation to the observable universe.

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Additional information

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Supplementary Information for

Nomogenesis and the logic of chance

Dmitri L. Vyssotski[1,2,3]

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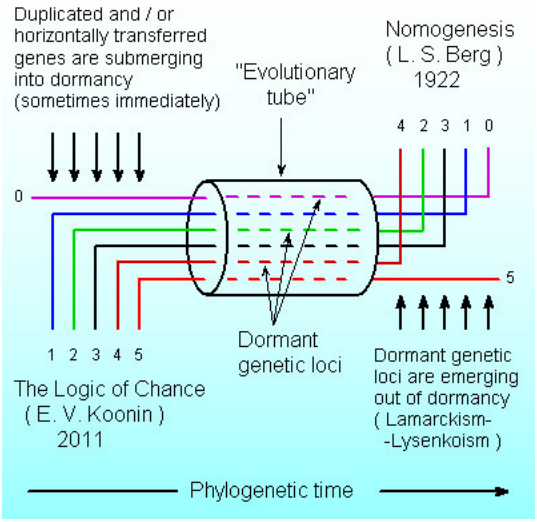
What can we say about "natural selection"? Natural selection, Darwinism and Mendelism were not mentioned in our article at all! Why? Natural selection can be represented as a weak and relatively long feedback in the system, as it was mentioned by Fred Hoyle (1987), p. 7[41]. The role of this long and weak feedback is negligible in evolution, and it was negligible during the whole history of life. Natural selection as a scientific theory is correct, because it describes real process that can be organized in laboratory or can be observed in semi-natural environment - see, for example, our article "Transgenerational epigenetic compensation and natural selection" (2014)[14]. However as a thought-style, it is deeply erroneous evolutionary teaching.

The term "thought-style" [*Denkstil*] was first introduced by Karl Mannheim in 1925[42]. However our understanding of "thought-style" is based on later publications of Ludwik Fleck – article "Some specific features of the medical way of thinking" (1927)[43] and book "*Genesis and Development of a Scientific Fact*" (1935)[44] [*Entstehung und Entwicklung einer wissenschaftlichen Tatsache: Einführung in die Lehre vom Denkstil und Denkkollektiv*]. At that time it was impossible to reveal evolutionary regularities of the thought-styles from the history of biology, but it was possible to do this with the history of medicine (the oldest branch of biology and one of the oldest branches of human activity in general).

Darwinism was found to be erroneous evolutionary teaching in 1885 by Nikolai Danilevski and it was demonstrated in his book "*Darwinism: A Critical Study*" (1885)[31-33]. The term "Darwinism", as well as, for example, "Mendelism", does imply nothing negative, no negative consonance. It is just a correct form for "teaching" or "thought-style" (Danilevski discussed this matter in the above-mentioned book and he also mentioned Russian equivalent – "мировоззрение"). For those who would like to add something emotionally negative, in order to underscore that we are talking about not just some "teaching", but about some "bad teaching", it is possible to switch to German-style: "*Darwinismus*" and "*Mendelismus*" (and everybody will see that it is something terrible).

Why natural selection can be called correct in its area of efficacy, but Darwinism is a deeply erroneous evolutionary teaching, erroneous thought-style? In modern science, it is usually assumed that relative importance of different factors can not be a matter for publication. And such approach is reasonable in the frame of one given thought-style, because everybody understands that under some conditions one factor will be more important, under some other conditions – some other factor, *etc*.

However if we are dealing with any movement from one thought-style to another one, the relative importance of factors



Supplementary Fig. 1 | Nomogenesis and the logic of chance. All currently available genomes illustrate the fact that the random change of genetic material was *de facto* the main modus of evolution (Koonin, 2011)[1]. Morphological changes in the evolution were introduced strictly on the basis of law (Berg, 1922)[2]. The appearance of new genetic elements in the genome and their appearance in the phenotype can be dissociated by unlimited number of generations.

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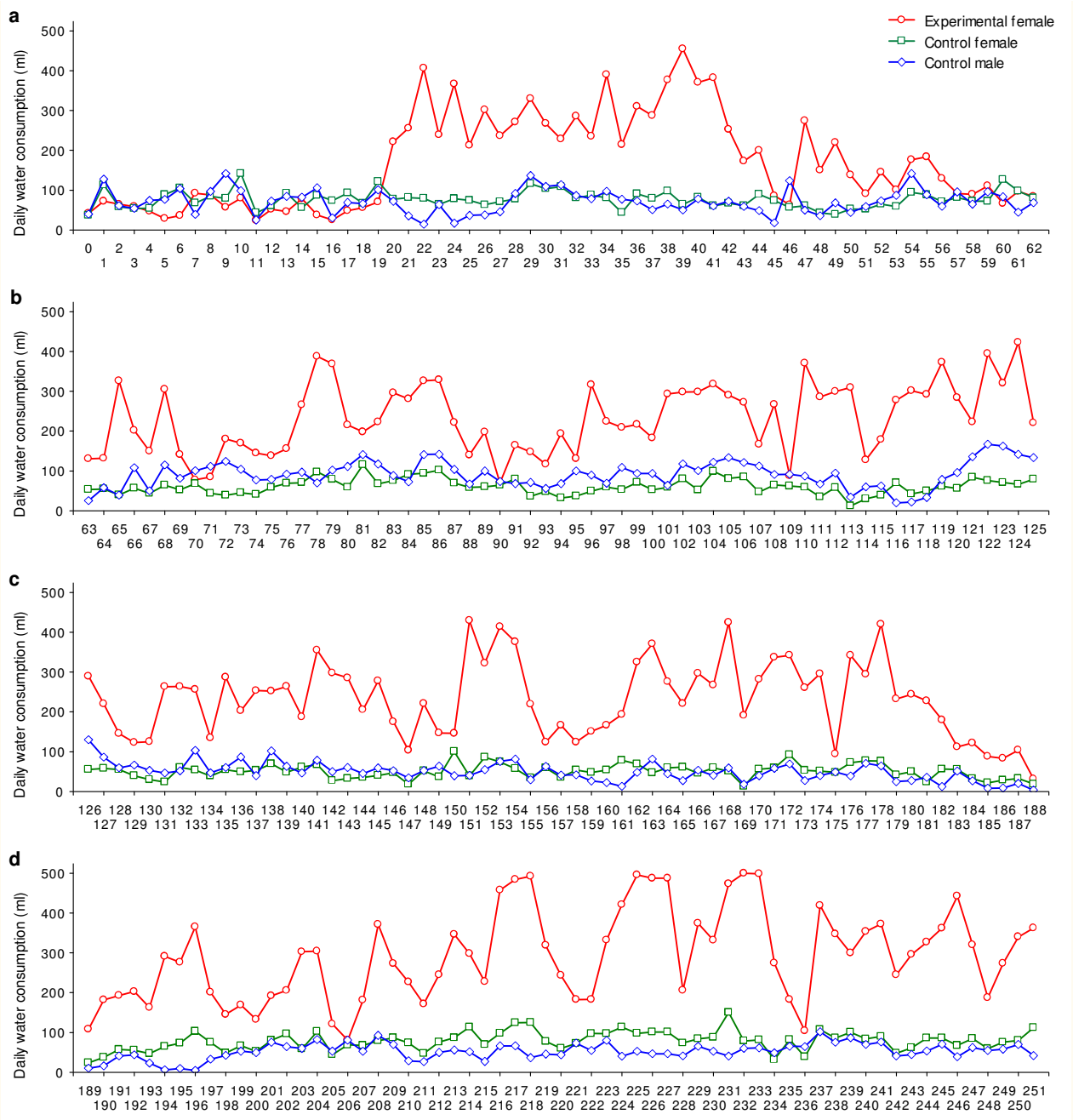


Supplementary Fig. 2 | Daily water consumption of F_1 female guinea pig, obtained from female with abnormally low adult water consumption and normal male (the 1st part of the record – 252 days). Note randomly expressed phenotypic inversion (the bursts of increased water consumption in this F_1 female *vs.* decreased water consumption in her mother). Postnatal days P614-P865 (2013-11-12 – 2014-07-21) are shown here. The next several months of the same record are shown in the next figure (**Supplementary Fig. 3**).

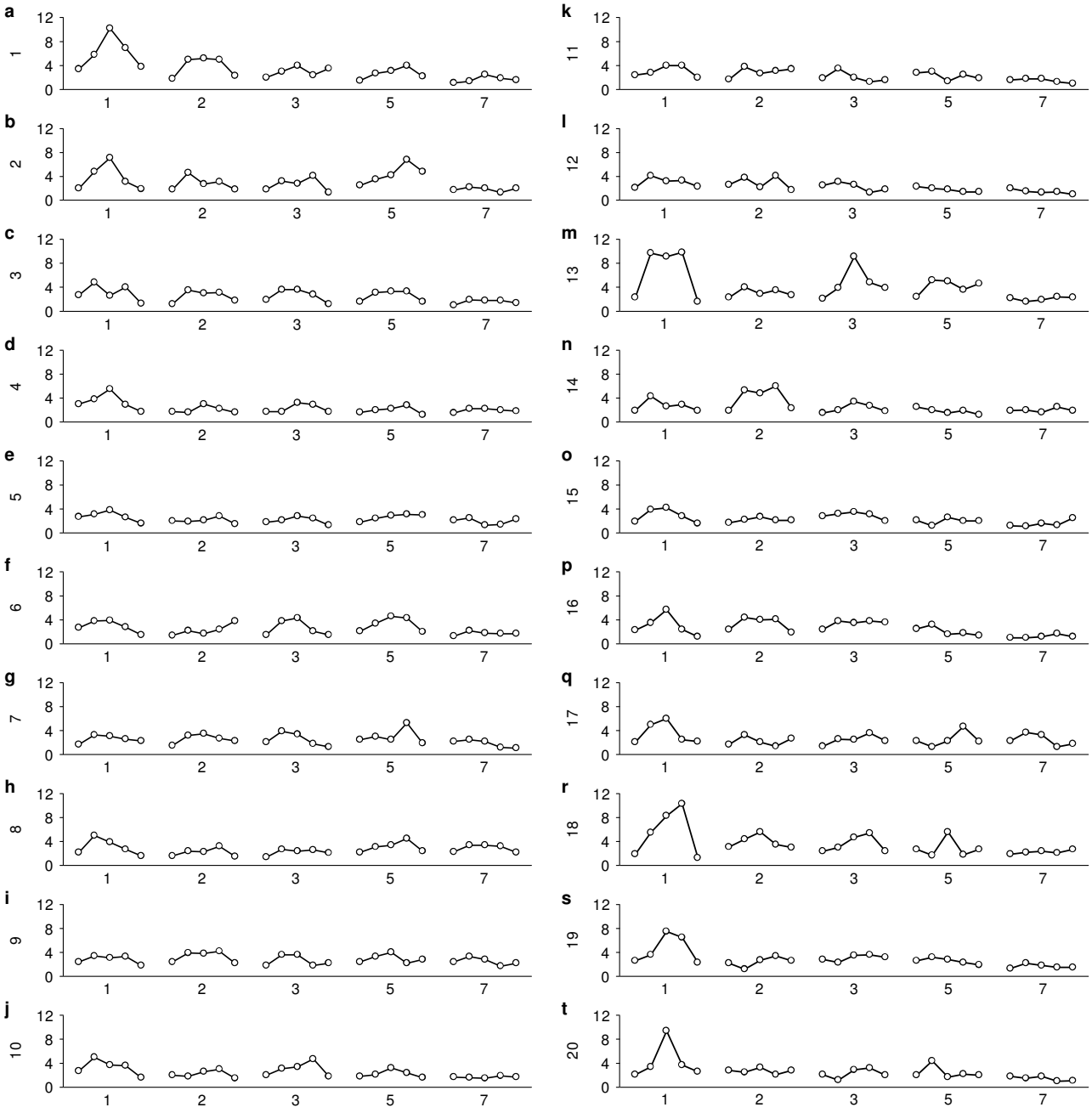
becomes crucial. Darwinism teaches us not only that some process (natural selection) can be observed in nature under some conditions, but that this process is the most important one in comparison with all other known and even unknown yet processes in this field (in the field of evolution in the case of natural selection). Mendelism teaches us not only that given factors are distributed in the progeny by known way (brilliantly described, for example, in the book of Arnold W. Ravin "*The Evolution of Genetics*", first published in 1965[46]), but that this distribution is the main law of heredity. It is automatically implied that if some other regularity would be found, it would be classified as "minor" from the beginning and until the end.

In real practice, if we see that some character was absent in both parents, but it has appeared in one descendant, it means that this character is a recessive trait and it was in heterozygous state in both parents, but in this given descendant it is in the homozygous state and that is why it is visible in the phenotype. However in the time of Darwin and Danilevski (before 1885), *i.e.* long before the rediscovery of Mendelism in 1900, some examples were known that were hardly compatible with

Supplementary Fig. 3 | Daily water consumption of F_1 female guinea pig, the 2nd part of the record – the last 252 days are shown. Previous part is given in the **Supplementary Fig. 2**. Postnatal days P866-P1117 (2014-07-22 – 2015-03-30) are shown here. In (**a**) ten days of the record are missed (*i.e.* water consumption was not measured) – P891-P900 (2014-08-16 – 2014-08-25) – due to SigmaCamp-2014 (www.sigmacamp.org) – summer science and math camp for students (age 12 to 16) where famous mathematician Maxim Kontsevich has given his lecture to all young participants.

Mendelism. Both Darwin (Vol. 2[46], p. 323) and Danilevski (p. 64[31]) discussed observation of Dr. Sichel (France) of one white cat with initially blue eyes that was deaf up to the age of four months, but then its eyes had become darker (common colour) and, simultaneously, the animal had acquired some ability to hear sounds. From the standpoint of Mendelism, it is difficult to say here that this animal was homozygous during its prenatal life and during the first four months of postnatal life, but then, suddenly, it occurred to be heterozygous in fact.

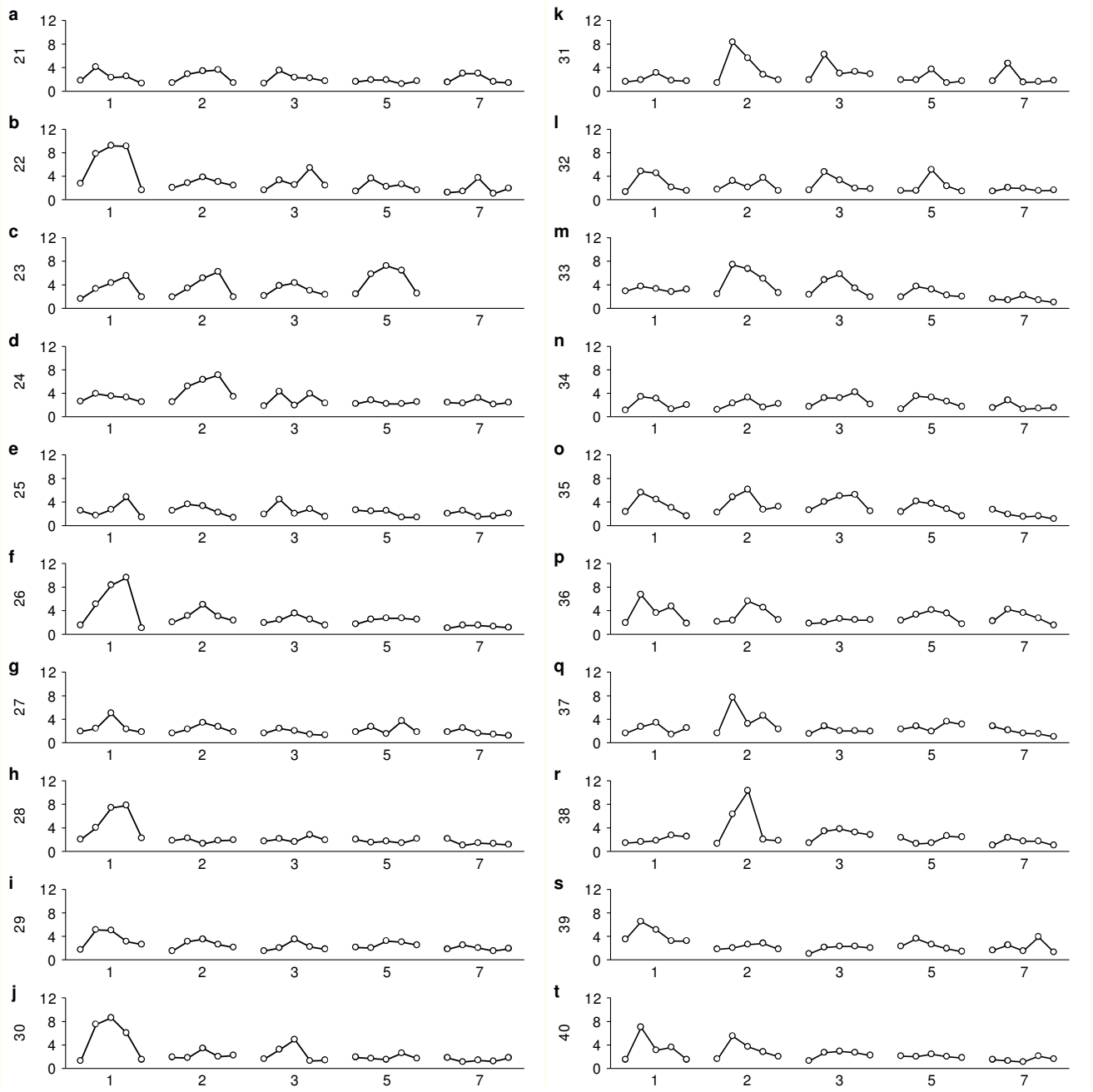
The management of dormant genetic loci by means of multiple and partially independent mechanisms has developed in evolution long before the appearance of sexual process and long before the appearance of Mendelian regularities. Multiple mechanisms that allow switching of any given genetic locus "on" and "off" came from the early evolutionary stage with rather intensive flux of genetic elements between all organisms, the flux that is unimaginable today among modern organisms. However all developed switches that at the beginning of life



Supplementary Fig. 4 | F_2 male Wistar rats, descendants of chronically morphine-treated males P and drug-naïve females. These F_2 males were obtained from F_1 females and F_1 males, whereas generation F_1 was kept drug-naïve until above-mentioned F_2 was obtained from them. Generation F_1 was obtained from chronically (P42-P79) morphine-treated males and drug-naïve females. Analgesic effect of morphine 10 mg/kg i.p. in the tail-withdrawal test (56℃) – tail withdrawal latency (s) is shown. The 1-st part of experimental group (20 rats) is shown here. The second part of the same experimental group (also 20 rats) is shown in the **Supplementary Fig. 5**. Control group (20 rats) is shown in the **Supplementary Fig. 6**. All shown rats received 10 mg/kg morphine daily during 7 days (i.p.). Analgesic effect was measured at days 1, 2, 3, 5 and 7. During each testing day the tail-withdrawal latency was measured once one minute before morphine administration (time point "-1") and 15, 30, 45 and 90 min after morphine injection, see **Supplementary Fig. 7**. Individual animals are shown in the **Supplementary Figs. 4-6**. Each animal is characterized by 25 measurements (5 days × 5 time points). Group curves (Mean) with statistics (Mann-Whitney U test) are presented in the **Supplementary Fig. 7**.

were comprised only from reversible genetic changes (and later some epigenetic switches could be added) are present today and they are more important for all evolutionary episodes, despite these evolutionary episodes are not so often events in a regular life of all organisms. All these switches are normally dormant *per se* in all subjects during their whole life, but can be revealed under extreme stress or unusual procedures (like prenatal, neonatal or adolescent paternal drug treatment).

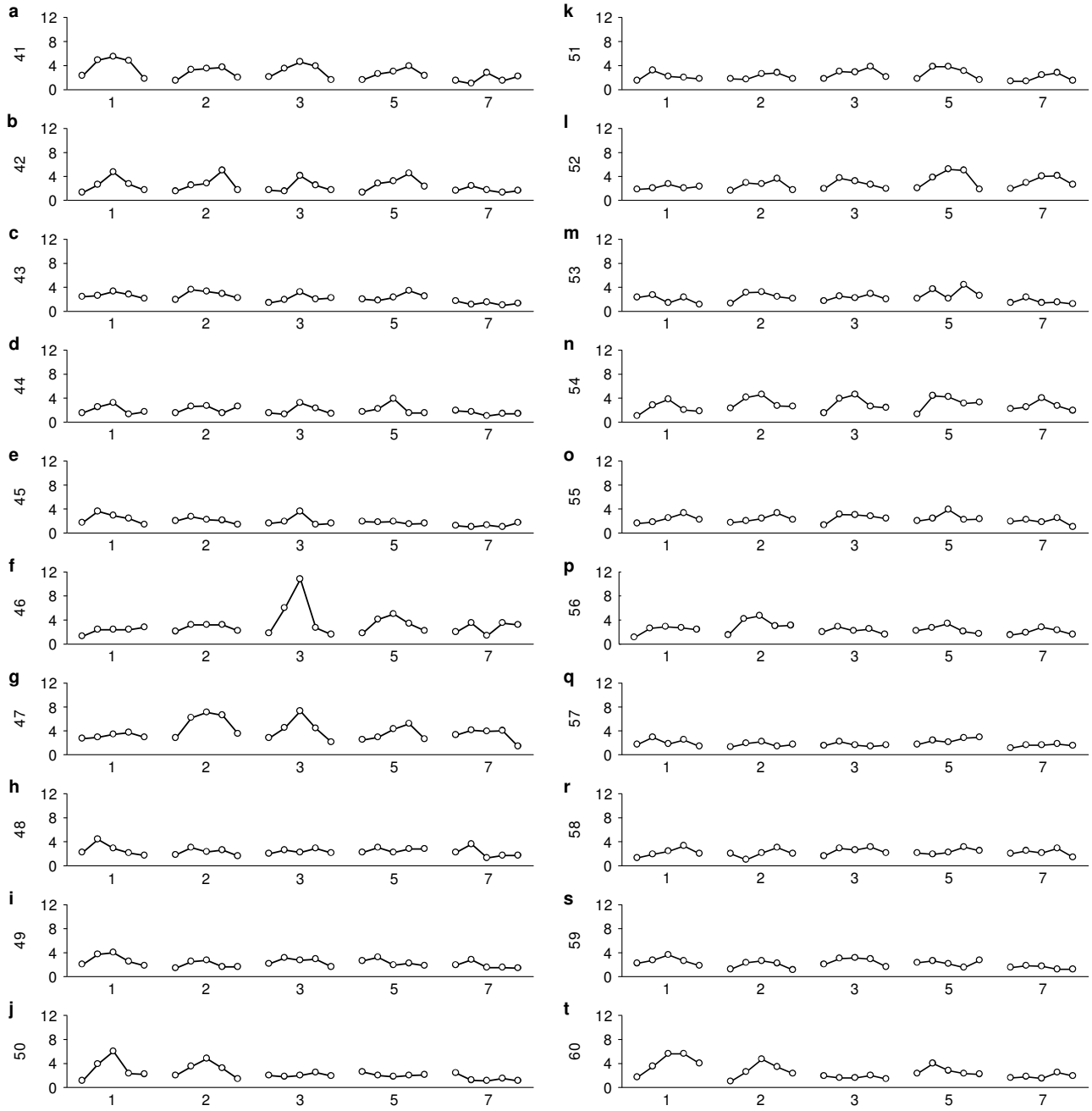
Many dormant genetic loci can be revealed and semi-randomly activated during the process of domestication as it was reported



Supplementary Fig. 5 | The second part of experimental group, shown in the **Supplementary Fig. 4**. Note that the vast majority of animals shows enhanced reaction to morphine during day 1, as it could be expected from the average curves, shown in the S**upplementary Fig. 7**. However some animals, namely ## 24, 31, 33, 37, 38 and # 14, have demonstrated the enhanced reaction to morphine only starting from day 2. Animal reaction to morphine is here "all-or-nothing" and average curves do not reflect this fact.

by Dmitry K. Belyaev[29,30] for domestication of silver fox. Random, unstable in time, expression of previously dormant genetic loci was their striking feature, observed and reported by D.K. Belyaev[29,30]. From the historical perspective we can say that dormant genetic loci (without this term *per se*) were discussed by Darwin in his theory of pangenesis[47], by Berg in his book "*Nomogenesis*"[2], by J.W. Harms when he discussed the transition of life from water to land, in his article (1929)[39] and book (1934)[40], and in more recent time by Zuckerkandl and Pauling (1962)[47]. The reversible genetic changes, that control the dormancy of genetic loci, can be revealed by means of bioinformatics, using available genomes, as it is shown, for example, in the **Supplementary Fig. 8**. Controllable genetic changes can be resolved from random ones. "Unstable, destabilized, heredity"[23], observable in the phenotype during the lifespan of a single organism, should have genetic basis.

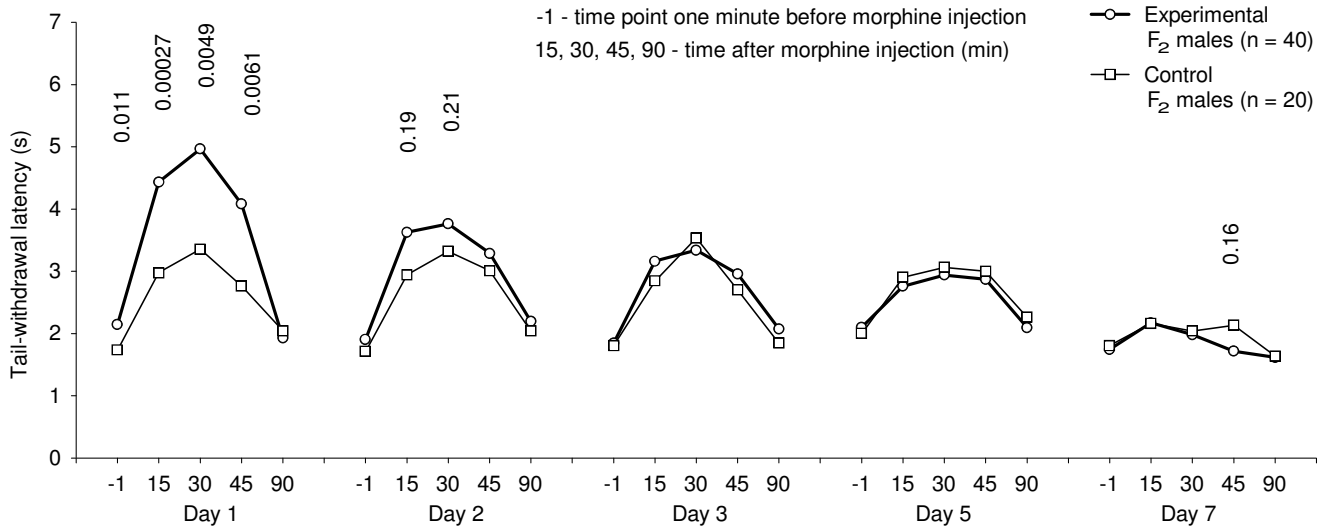
In the **Fig. 7**, where the processes in the modern organisms are shown, the stochastic fluctuations in gene expression are very important for selection of one dormant gene among many-many other dormant genes, for selection that makes only this particular



Supplementary Fig. 6 | Control group of male Wistar rats, synchronously obtained and tested with experimental ones, shown in the **Supplementary Figs. 4** and **5**. Control animals show smooth curves without any enhanced morphine-induced analgesia. However even among control animals there is one, namely # 46, that suddenly has shown enhanced sensitivity to morphine-induced analgesia at day 3. In general, the paradoxical behaviour, appearing randomly in time, is not typical for control animals.

genetic locus open for further regulation of its expression. For *Metazoa* (all multi-cellular organisms), the stochasticity in expression must be present not only at the level of a single cell, but at the level of the whole organism, all cells of given organism. Macroscopic stochasticity is achieved by fluctuations (relatively slow fluctuations) of hormone levels, including stress-hormones, sex-hormones, and many other hormone-like substances that may provide oscillations of gene expression at the level of the whole organism.

Many asynchronous oscillators, macroscopically modulating expression of many different genes, are really necessary for multi-cellular organism. The reason is (see **Fig. 7**) that protein A that increases probability of reversible genetic change towards activation of genetic loci and protein B that increases probability of reversible genetic change towards deactivation are not specific with respect to many-many dormant genes – they work about similarly for any gene from this gene group. And functional systems of the organism those are experiencing significant



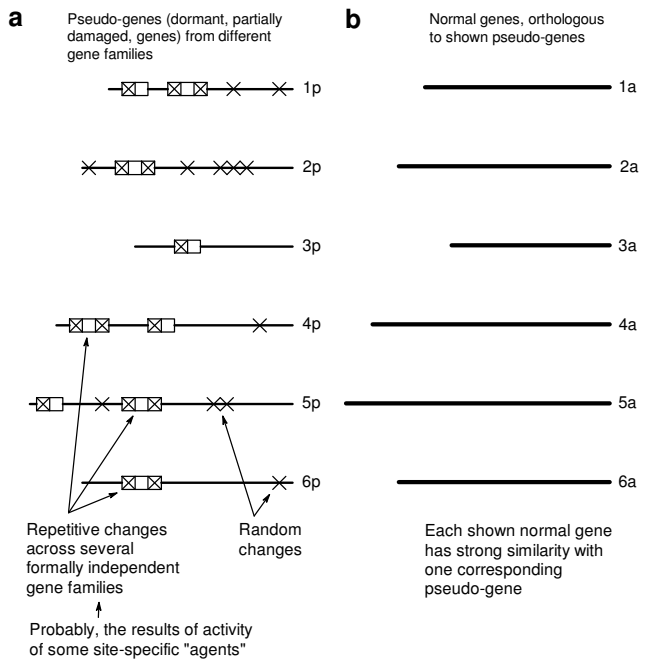
Supplementary Fig. 7 | Averaged curves (mean group values) of the results shown in the **Supplementary Figs. 4**, **5** and **6**. Analgesic effect of morphine (10 mg/kg, i.p.) in the adult (P65 at Day 1) F_2 male Wistar rats, descendants of chronically (P42-P79) morphine-treated P males and drug-naïve P females (previous generation F_1 was kept drug-naïve until above-mentioned F_2 was obtained from F_1 females and F_1 males). Note that the suppression of the enhanced sensitivity to morphine-induced analgesia was developing during days 1-3 and it can be seen only in the experimental animals. However the development of classical tolerance was identical in control and experimental rats and it was observed mainly during days 3-7. The processes around previously dormant genetic locus and the development of classical tolerance to morphine are distinctive and temporally separated processes. This is useful observation, but it is not the most important one. The most important one is completely masked by the averaged curves: the expression of previously dormant genetic locus is strictly binary ("all-or-nothing") and it is fundamentally stochastic in time during the lifespan of a single organism ("unstable, destabilized, heredity"[23]). Mean. Mann-Whitney U test.

difficulties in their functionality, those have problems detectable at their action acceptors, do not have any direct link to specific or potentially useful dormant genetic loci. Thus, the loci should be activated asynchronously, in a semi-random asynchronous fashion (because their literal one-by-one activation is not realistic), seriously modulated by macroscopic hormonal fluctuations. The dispersion in time of expression of previously dormant genetic loci, the dispersion during lifespan of a single organism, is absolutely necessary. And this process of macroscopic fluctuations and dormant loci activation-deactivation will be stopped as soon as the problem on the action acceptor of the problematic old functional system of the organism will not be detected anymore – it will be eliminated or significantly attenuated by activation of one previously dormant genetic locus.

Note that in all publications about transgenerational epigenetic compensation[10-14] the phenotype of the progeny is always gender-dependent (it depends on sex hormones) and it is often previous-stress-dependent (it depends on stress and previously experienced stress of given descendant). It means that all newly accessible for expression previously dormant genetic loci are already equipped with sensitivity to sex-hormones, stress-hormones, and may be sensitivity to other hormone-like substances (their expression is immediately modulated by all above-mentioned hormones). And such situation is not only present in all multi-cellular organisms, but it is required by the evolutionary mechanism of orthoselection, conducted by old functional systems (by their action acceptors). "Orthoselection" is selection of one necessary locus among all or many dormant genetic loci of the organism. The term "orthoselection" [*Orthoselektion*] was originally used by Plate (1913)[48] in strictly phenotypic sense. Its meaning was further developed or *de facto* modified by Harms in 1929-34[39,40], see p. 201[40]. However in our text the meaning of this term is modified further even with respect to understanding of J.W. Harms.

In *Metazoa* the sensitivity of the expression of previously dormant gene to hormonal pseudo-random oscillations is necessary requirement that should be fulfilled in order to be selected. The genetic locus should have this property in order to be selected from completely dormant state into the state, opened for further regulation of expression.

The same sensitivity to hormones makes possible the presence of important additional process – selection of germ cells (spermatozoa) with the presence of particular activated previously dormant genetic locus. Similar, but not identical, idea was introduced by August Weismann under the title "germinal selection" (1896)[49]: Weismann has proposed separate semi-independent selection of different genetic loci (determinants) of the genome, which currently is shown to be technically impossible. However similar process, if it is conducted only with respect to one active previously dormant genetic locus, is not only possible, but it will be highly efficient. The important requirement is that the spermatozoon that is bearing particular genetic locus in a newly opened state should have high probability to be involved. Thus, the physiological state of all spermatozoa must be modulated by hormones and the expression of particular gene of interest must be modulated by the same hormones as well. So, in this case given combination of hormones will be able to select gametes, during some stage of their development, with recently activated previously dormant



Supplementary Fig. 8 | The dormancy of pseudo-genes is promoted by several distinctive classes of genetic changes. The comparison of pseudo-genes with orthologous genes across several independent gene families can reveal several universal site-specific changes, potentially responsible for dormancy. Several classes of more or less universal genetic changes are present in pseudo-genes in addition to purely random mutations. If some of the site-specific repetitive genetic changes in pseudo-genes are potentially reversible, *e.g.* reversible with a help of specific proteins, these pseudo-genes can be brought out of dormancy by combination of some external and internal factors (still unknown combination).

dormant genetic locus. Note that, in comparison with old idea about selection on the basis of all genes, presented in the genome of each spermatozoon, the selection on the basis of one locus is not only possible, but can be done with relatively high efficacy.

The selection of germ cells was always attractive, because ½ of parental genetic information is lost with respect to given descendant anyway – so, the process of their selection would have zero cost factors. A combination of orthoselection (activation of one dormant genetic locus) with germinal selection (gametic selection of spermatozoa with newly activated genetic locus) produces the same hopeful monsters that were described by Richard Goldschmidt in 1933[50] and 1940[51] and the same evolution "*en masse*" that was described by Leo Berg in 1922[2] (all individuals in population are evolving simultaneously – if they have the same dormant genetic locus, involved in current evolutionary episode, in their genomes).

Horizontal gene transfer was even more important for evolution at its previous stage than for evolution of known prokaryotes. The idea about horizontal gene transfer as an interesting potential possibility was discussed in the sixties, for example in the book "*The Evolution of Genetics*" (1965)[45]. But only Boris Mirkin and Eugene Koonin have shown on the basis of available genomes that this possibility was *de facto* widely realized in the evolution of prokaryotes[52,53]. There is a difference between the theoretical possibility of the process ("pure possibility") and the frequency of its practical implementation ("real probability"). It was shown by Mirkin and Koonin that the probability of horizontal gene transfers in evolution of currently available prokaryotes was indeed really high.

As we can see here, all known Mendelian laws are clearly applicable to the observable reality, but Mendelism as an overwhelming thought-style in the field of heredity is deeply invalid. The same we can say about Darwinism: natural selection, as a long and weak feedback, is observable in nature, but the role of short and strong feedbacks, formed by action acceptors, is dramatically higher. Strong and short feedbacks, driven by action acceptors, were important for evolution even before the appearance of any more or less reliable replication (the process of collection of pseudo-copies by action acceptors was used instead), before the appearance of more or less reliable Eigen cycle[34]. And the role of Eigen threshold[34] itself occurred to be diminished by the action acceptors up to barely important level, and, thus, the time point of the beginning of "biological evolution" occurred to be diffused.

Darwin's algorithm (natural selection) is not the only one that can provide purposive output (useful structures) from random input (stochastic mutations and stochastic events in general). Other algorithms are not only possible, but some of them, *e.g.* the one that is shown in the **Supplementary Fig. 1**, are much more efficient.

How does the teaching that is so erroneous, could be so dominant during more than 150 years and could be described by so many humans in so positive colours? Let say "the main idea of biology", "the basis of modern biology" – just a few examples. However from the history of human civilization we know at least one event with similar properties – the origin of Christianity about 2000 years ago. Among other features, some of which will be discussed later, the relative simplicity of the teaching was the key to its fast propagation. Both Christianity and Darwinism have brought nothing positive in comparison with previous thought-styles. In 1885 Nikolai Danilevski has compared the propagation of Darwinism with the propagation of Mohammedanism (Danilevski used here Russian word "магометанство", so our translation is as precise as technically possible, contrary to the term "Islam"). Pointing out that the fast propagation of Darwinism can not be considered as an indicator of its superiority in any dimension, except simplicity, Danilevski has noted that Mohammedanism had faster speed of propagation than Christianity. Please note that this observation was done not today, but in 1885.

Darwinism has direct impact upon current understanding of social reality. Modern social propaganda is widely using the term "equality", like "racial equality", "sex equality", *etc*. It is silently implied that in order to have equal opportunities (today or in the future), all humans should be equal, because otherwise some of them will be eliminated by evolution and only the rest will be evolving – inevitable consequence of natural selection. Indeed, differential survival can be observed in human population, but it has no relation to evolution of any nationality, any race, or human population in general. Sometimes modern social demagogues are speaking about important difference between Darwinism as a scientific theory and so-called "social Darwinism". However there is no such difference (and it never was) – Darwinism and social Darwinism comprise/share exactly the same thought-style.

Some group of individuals can become extinct, but not due to evolution in the form of natural selection, *i.e.* due to competition with other groups. Some group could be extinct due to inefficient mechanisms of evolution, inefficient functionality of action acceptors and poor efficacy of local feedback loops that are the main effectors of evolution in any species. All species can be evolving, each with different rate, even without any competition at all (*i.e.* no competition between different species and no competition between individuals inside any given species is specifically required). The idea of current social propaganda that in order to be equally evolving all individuals should be equal has no material basis and it has no relation to the observable evolutionary process. Even very different nationalities and races can evolve successfully being very different in all measurable dimensions.

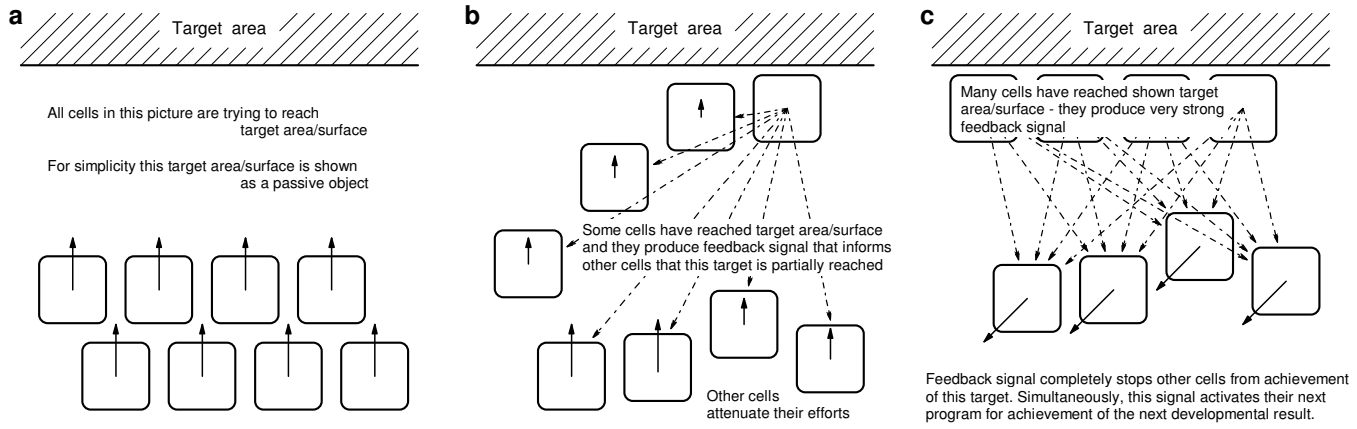
Charles Darwin and modern Darwinism. Our opinion about Darwin is solely based on the texts of books, written by him, mainly "*On the Origin of Species*" (1859)[54] and "*Domestication*" (official title: "*The Variation of Animals and Plants under Domestication*", 1868)[46]. Darwin did an attempt to understand nature. And he has proposed really existing mechanism in the form of natural selection that could be a basis for evolutionary process. However the evolutionary process has chosen different route from the early beginning. It does not make Darwin and Darwin's attempt less respectful, but all further known behaviour of Darwin's followers, including relatively recent proponents, is really disgustful. In the discussion of Koonin's article "The cosmological model of eternal inflation and the transition from chance to biological evolution in the history of life", published together with this article in 2007[55], we can see fine example when reviewers of this article recommend to use and to promote obviously false statements in order to win discussion with proponents of "Intelligent Design". Intelligent Design is a branch of Christian thought-style, and as such it has nothing common with our own one, where Orthodox Judaism remains undisputable etalon during many centuries. However it would be necessary to mention that modern Darwinism *de facto* does not have any solution to the problem of "irreducible complexity" that was crystallized in the frame of Intelligent Design (Darwinism not only can not provide any satisfactory solution, but it can not provide any solution at all). Thus, proponents of Intelligent Design, in spite of being Christians, are right in the discussion with Darwinists concerning this question of irreducible complexity. Darwinists do not have any solution to the problem of the origin of life as well. We should be grateful to proponents of Intelligent Design for their help. As a rule, Darwinists identify themselves with "scientists", at least in discussion of "science" and "religion", – and it is the most disgusting thing. The substitution of "evolution" with "natural selection" is a purposively misleading step, even if further interaction with religion is discussed in positive tone, as it was done by Theodosius Dobzhansky[56]. Danilevski, Bergson, Berg, Harms, Goldschmidt, Altshuller, Anokhin and Koonin have very different opinions about evolutionary process – and all of them are much more researchers/naturalists than modern Darwinists.

All mathematical modelling and methodology developed for natural selection has no value for evolution and it can be taken only as a nice exercise in mathematical methods, because it covers only very weak and insignificant branch of evolutionary process (note, however, that purifying selection remains relatively important, as it was mentioned by both Berg[2] and Koonin[1]). For modern scholars (see book of Joseph Felsenstein "*Theoretical Evolutionary Genetics*", editions from 1978 till 2015[57]) it is very difficult to recognize that natural selection is really existing process in nature and, simultaneously, it is deeply erroneous evolutionary teaching, irrelevant to the route, chosen by nature at the beginning of life and still actual.

There is a notion that the final goal of evolution of all matter in the universe is development of consciousness – so-called strong anthropic principle. From the standpoint of our current knowledge about the existing functional systems with their ability to anticipate and to build up their future, the appearance of consciousness as the next extension of some the most complex functional systems has solid basis. So, yes, the appearance of consciousness is the final goal of the evolution of universe.

At the beginning of life an action acceptor was a piece of double-stranded DNA, capable to bind one useful component. It sounds like vulgar materialism (Ludwig Büchner, 1855[58]). Simultaneously, action acceptor is a structure that anticipates the future or, at least, it was introduced for this purpose (Peter Anokhin, 1955[3]). Extreme idealism, for example in the form of creative impetus (Henri Bergson, 1907[59]), remains solid part of our thought-style. Extreme idealism and vulgar materialism are not compatible with each other and this incompatibility (contradiction) does not allow any intermediate ("optimal") solution. However this contradiction may have solution in time (see below). An idea, as an object from the ideation space, at the moment of its perception selects neural cells those occurred to be compatible with it by chance (Gerald Edelman, 1987[60], 1993[61]). The structure of an idea is dictated by the laws of the ideation space and the last ones do not have any material limitation, neither real, nor imaginary; it is sufficient to say that the idea is an external entity with respect to given organism at this given moment. The complexity and temporal structure of an idea is unlimited. And this is idealistic part of the natural process – the evolution of ideas may have no interference from the material world. As soon as group of cells has been selected, the next step in evolution of this idea is determined by the internal features of these cells. The next modification of this idea is a product of these selected cells (and some cells around) – exactly in accordance with vulgar materialism. As soon as an idea or modified idea is ready to return to the ideation space – it is completely idealistic entity, ready for the next perception by the next or the same leaving creature (not necessarily human). We can see here only vulgar materialism and extreme idealism, self-separated in time. Is their interaction – so-called "consciousness"?

It is rather obvious that the ideation space has important impact upon human evolution and behaviour, perhaps more important than all material factors taken together. The process of the acceptance of an idea and the further development of this idea are two absolutely different processes, requiring absolutely different kinds of neural plasticity and having absolutely different time-scales. Sometimes, the lack of learning abilities can be partially compensated by overexploitation of abilities of modification of previously accepted ideas. It concerns only relatively simple tasks. And this process requires more time and it is less efficient. In general, both capabilities are required in well-developed state.



Supplementary Fig. 9 | Cell differentiation in a multi-cellular organism (*Metazoon*). **a**, Non-differentiated population of cells. All cells are trying to reach the same state or target – all of them have the same program. **b**, The target is reached by some cells – due to stochastic reasons and variability in cell movements. The successful cells produce feedback signal (*e.g.,* soluble substance) that stops other cells from reaching the same target and switches their efforts to the next step of their internal program. **c**, The differentiated state is shown clearly. The successful cells are serving as "evocator" or "inductor" – they induce the next developmental processes in other cells. And it is impossible to say whether the involved feedback is positive or negative, because it is positive and negative simultaneously – it is negative with respect to the achieved state (it blocks further attempts to achieve this target), and it is positive with respect to the next developmental state (because it switches the cells to the achievement of the next target). The situation is even more interesting. When the number of successful cells is small – the feedback is positive or it is interpreted by the receptive cells as positive (or someone can describe this feedback as "insufficiently negative feedback"). When the number of successful cells is large – the feedback is negative or it is interpreted as negative by the receptive cells. However in the both above-mentioned cases the feedback remains logically the same and it can be even the same soluble substance (but in different concentrations). The above-mentioned mechanism entails fantastically stabilized or canalized ontogenesis. And the above-mentioned canalization is achieved by internal means – by means of action acceptors that sense feedbacks from current developmental processes. Previously known terminology like "lateral inhibition" and "negative feedback" is only partially correct. "Action acceptor" provides more precise understanding of an episode of differentiation. In order to change differentiation, one has to add or remove at least one action acceptor.

In the **Supplementary Fig. 1** it is shown that such process as activation of dormant genetic loci is explained or associated with such direction of thought as "Lamarckism-Lysenkoism". Lysenkoism is serving as a nice example of pseudo-science during the last 50 years, at least. However the situation with Lysenkoism becomes not so grotesque, if our attention becomes focused exclusively upon the texts, written by Trofim D. Lysenko in person. Many examples, accumulated by Zhores A. Medvedev in the book "*The Rise and Fall of T.D. Lysenko*"[62] as "ideas of Lysenkoists", are out of discussion, because they can not be found in Lysenko's manuscripts, specifically in "*Agrobiology*"[23], published in English during Lysenko's life time. The differences between classical Lamarckism and Lysenkoism can be found in the article "The situation in biological science", pp. 515-554[23], first published by Lysenko in 1948 (in English – in 1949). These differences can be summarized the following way.

1. Heritable and non-heritable components of an acquired character. An acquired character, as a result of the process of its acquisition, is divided into heritable and non-heritable components. The transmission to the descendant of the only heritable component(s) induces the phenotype that differs from both control and parental phenotypes (*i.e.* the descendant has "the third" phenotype – "new", partially unexpected, phenotype). "Numerous facts go to show that changes in various sections of the body of a vegetable or animal organism are not fixed by the reproductive cells with the same frequency or to the same extent" (p. 535[23]).

2. The importance of the history of acquisition of an acquired character. The nature and expression of phenotype in the descendants depends not only on the presence or absence of "acquired character" in their parent(s), but on the history and temporal dynamics of the process of acquisition of given acquired character by parent(s). It means that the presence of an acquired character in the parents can not guarantee the appearance of any of its components in their descendants, because the dynamics of acquisition is very important also. For example, only treatment during specific developmental stages of parent(s) can be effective in production of modified progeny.

3. "Unstable, destabilized, heredity". The phenotype of a descendant, obtained from treated parent(s), is unstable in time during lifespan of a given descendant and during several consecutive generations after. It means that even if some unusual phenotype will be observed in the descendants, it will be observed not in all experimental animals, and during lifespan of a single animal it can appear during quite random time periods and this appearance can be modulated by rather random external factors. The term "unstable, destabilized, heredity" [in Russian: "расшатанная наследственность"] was not invented by T.D. Lysenko, – in accordance with his own statement (1940), he has accepted these views after Vilmorin, Burbank and Michurin (p. 298[23]). However it was Trofim D. Lysenko who has investigated the conditions (p. 537[23]) when "heredity becomes extremely unstable" – at that time without any reference to "dormant genetic loci". The term "genetic locus" in given context was introduced much-much later by James A. Shapiro (2011, p. 30[63]).

Lysenko's statements were based on organism's phenotype. Vavilov's law on homologous series in variation[25] is also a phenotype-based generalization (it does not mean that it is "bad", it means only that homologous series in variation can be revealed by different means, *e.g.* they can be observed in F_1 hybrids, see pp. 73[26], 82[26]).

These additions or modifications of classical Lamarckism, introduced and/or strongly supported by Trofim D. Lysenko, were confirmed in mice, rats and guinea pigs by experiments with paternal drug treatment (including recent ones)[6-14]. That is why the activation of previously dormant genetic loci in evolution is marked as "Lamarckism-Lysenkoism".

The question about localization of heredity, discussed by Lysenko, is not so simple as well. Lysenko did accept the role of chromosomes in heredity, the role of germ cells, but, in addition, he linked heredity with all other components of the germ cells and with all other cells of the organism. We know that any multi-cellular organism is covered by a net of multiple feedback loops, including germ cells. Mechanically, heredity is localized in the chromosomes of the germ cells, but many events on the periphery have about the same level of functional importance, due to the presence of feedback loops, involving the germ cells.

There is also notion in the literature that "Lysenko together with all his ideas" has appeared from nowhere (*e.g.* as a barely literate peasant) – "from nowhere" not in a historical dimension, but in an ideation space. This notion is promoted by those researchers who never pay attention to the books, rejected by contemporary science, for example books written by Danilevski (1885)[31-33], Bergson (1907)[59], Berg (1922)[2], and alike. Only in this case the ideas of Lysenko are appearing from the middle of nowhere. By the way, Charles Darwin has written the following about Philippe André de Vilmorin (Vilmorin was mentioned by Lysenko as the first one who has described destabilized heredity): "The most celebrated horticulturist in France, namely, Vilmorin, even maintains that, when any particular variation is desired, the first step is to get the plant to vary in any manner whatever, and to go on selecting the most variable individuals, even though they vary in the wrong direction; for the fixed character of the species being once broken, the desired variation will sooner or later appear" (Vol. 2[46], p. 250).

The next to last figure in this Supplementary Information, **Supplementary Fig. 9**, illustrates the role of feedback in cell differentiation in a multi-cellular organism. Shown schema of differentiation is not new – it was discussed in 2004, in the book "*Elements of Biological Concepts*"[18]. It remains important, because only feedback loops can provide necessary canalization of ontogenesis during cell differentiation (its resistance to external and internal fluctuations) that is so important for correct individual development of any *Metazoon*. Well-known from the "*Molecular Biology of the Cell*" (Fifth Edition, 2008)[64] concepts of "lateral inhibition" (pp. 1314-1315[64]) and "positive feedback" (pp. 1314-1316[64]) provide only partial understanding.

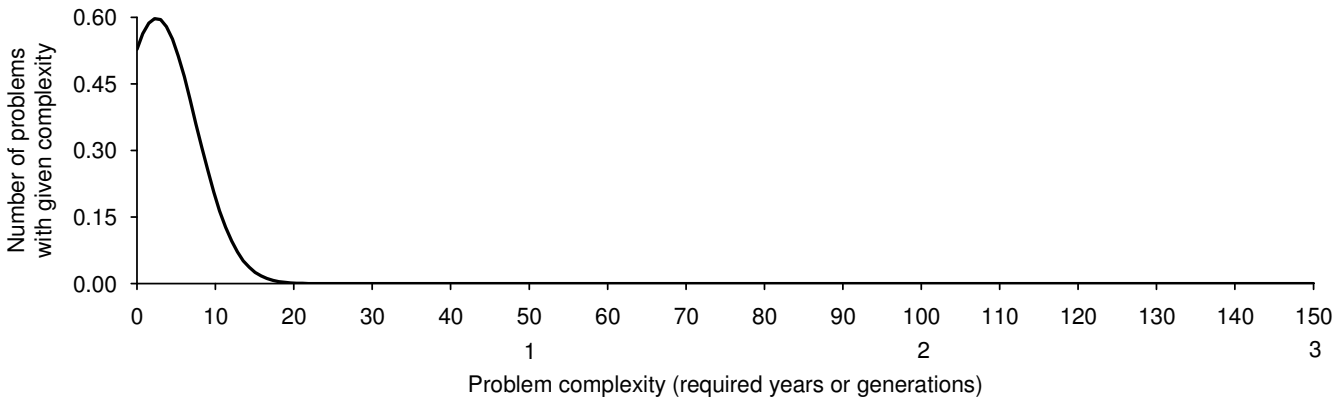
Biological concepts are important attempts to accumulate and develop current biological knowledge. Up to now all biological concepts, accepted as a steps in development of our knowledge, belong to one single thought-style. Current social propaganda in science forces us to assume that there is one "scientific" thought-style, a "true" type of behaviour, and other thought-styles, like "pseudo-scientific", "meta-physical", "religious", and alike. Karl Popper[65-67] has introduced "criterion of demarcation" between "science" and "meta-physics" and it remains rather popular in different circles in the field of biomedical research. As it will be shown later, any distinction between science and pseudo-science is counter-productive (it does not work in real time and post-hoc it provides only illusions).

Now we are going to discuss not only evolution of concepts, but evolution of thought-styles in biological science. All concepts or attempts to understand observable and not so observable biological reality are distributed between three classes: 1) accepted concepts (really scientific and important knowledge that is still with us: Darwinism, Mendelism, DNA structure and replication, a lot of other not so famous concepts); 2) currently rejected concepts, but previously accepted by majority of researchers as potentially correct (these concepts comprise so-called "history of science" or "just a history"); 3) rejected concepts, immediately rejected, anti-scientific or pseudo-scientific concepts (this knowledge has no real value for modern science: nomogenesis[2], hopeful monsters[50,51], dormant genes[39,40,47], germinal selection[49], many others – nobody even remember about their existence [not really "nobody", because there are "somebody" who do not completely share the thought-style of current scientific propaganda, *e.g.* religious Jews]).

Briefly speaking, for current social scientific propaganda there are: 1) science (an important part); 2) history of science (just a history); 3) garbage or pseudo-science (of no importance). Not everybody is sharing this official scientific thought-style and among researchers who have proposed something in person this thought-style was never popular (see, for example, article of Zuckerkandl and Pauling, 1962[47] – its last pages are very interesting and hardly compatible with straightforward expectations, associated with Pauling's name).

All modern methodology of science is optimized for tasks with complexity around 2 ½ years or less (**Supplementary Fig. 10**). The evolution of a thought-style in the form of its replacement requires 100 years or more and such event as a change of thought-style is not traceable in biology during previous 150 years – it is absent in the accessible history. However the evolution of thought-styles was possible to investigate in medicine, where the accessible history in much longer – and it was done by Ludwik Fleck in 1927-1935[43,44]. Thus, we can obtain more detailed information about regularities of evolution of biology from the evolution of medicine than form time-limited history of biology. Similar to this, we can obtain much more detailed information about evolution of functional systems in living organisms looking at evolution of technical systems, where their construction is much better documented – and it was investigated by Genrich Altshuller in 1956-1985[68-70]. It was shown to be wrong that technical systems are evolving in accordance human "wish" (popular erroneous notion). Technical systems are evolving towards higher efficiency through solution of technical contradictions – where the improvement of one feature leads to degradation of other useful feature and the next invention breaks this contradiction down. Optimization in the frame of any chosen schema is relatively non-important for evolution (however it is important for living organisms and for users of technical systems).

Supplementary Fig. 10 illustrates not only that the existing problems may have different complexity, but that our knowledge of simple problems is useless with respect to problems that require 50 years or more. What is known about evolution of



Supplementary Fig. 10 | Distribution of problems in modern science in accordance with their complexity (required years or generations of researchers). It is not specified whether this complexity is "objective" or "subjective". The fact is that typical good problem requires about 2 ½ years in order to be solved by a person. The problem that requires 5 years is obviously more difficult than average. The problem that requires 10 years or more is the area fore monsters or maniacs. And the peculiarity of the situation is that not only any positive reinforcement will be absent during these more than 10 years, but any feedback from the result will be absent also – it will be unclear whether all attempts are done in correct or completely wrong direction. And when the solution of the problem will be obtained, all previous attempts will be classifiable with ease. However all these attempts will not be useful anymore – they will be just a part of the history.

thought-styles is that they are incompatible with each other. It means that from the position of current thought-style we can say nothing good about the next thought-style and we can say nothing good about all attempts to develop the next thought-style. All these attempts are looking pseudo-scientific. Any criterion to distinguish "science" from "pseudo-science" is good for nothing, because the new thought-style is not only looking pseudo-scientific, but it is pseudo-scientific in accordance with standards of current thought-style (at least, it was so in the history of medicine, and we have no reason to assume that in the future history of biology we will see something else).

However the problems that require 2-3 generations are being solved somehow… By means of "creative impulse" of Henri Bergson, going "through centuries", or by means of some other idealistic matter (we already know that any feedback for the first 2 generations is absent in the material world – not only material reinforcement, but any information about the value of an attempt is absent also). The philosophy of the process requires us to keep all honest previous attempts, all attempts done in a non-gentile style. These attempts should be accessible without any relevance to something reasonable (we already know that the majority of these attempts, including the most important ones, will be looking non-reasonable and anti-scientific). The next generation has to develop any given attempt further, even if any local sense of such development is missing (to develop this attempt further just because this attempt was done). The static part is even more important than dynamic part, because dynamic part can be totally absent during two or three generations – nothing really bad will happen, but the static part that holds all previous attempts is crucial for the whole future history (see: Bergson, H. *The Two Sources of Morality and Religion*, 1932[71]). Only idealistic, traditional religious approach can be the driving force for problems that require more than one generation to be solved. It is not a secret that in modern scientific circles any religion is associated with its static part only, whereas dynamic part of religion, where humans are reading books written by other humans and are trying to solve problem, formulated (and sometimes already partially solved) in these books, and are trying to write the next books, is completely missed. And it is completely missed that a problem, being formulated, contains already about 50% of its solution, if it is a difficult problem (subjectively difficult or objectively difficult – it does not matter here, it is important that it can take more than 40 years). From this standpoint, a book that contains non-solved problem is even more important than a book with successful solution of some relatively simple problem, but it is so only for individuals who can work in traditional religious thought-style (nobody will pay for this work, of course). These ideas are not new, as we already can imagine, and they are provided by the following books – let's take only three examples, but others can be added: Bergson, H. *Creative Evolution*, 1907[59]; Altshuller, G.S. & Vertkin, I.M. *How to Become a Genius: The Life Strategy of a Creative Person*, 1989[72]; Vyssotski, L.L. *The Technology of Achievements*, 2011[73]. The last two books are not translated into English yet, they contain a lot of real historical examples and due to this reason they hardly can be commercialized in the USA, because the "genius" here is not equal to "successful person", but it is the person that can be artificially added to the category of "successful persons" only sometimes (typically – post-mortem).

Of course, religion is a serious matter, but simultaneously it is a game or a play, but the game and the play that forms the thought-style, and the only one that is productive on a time-scale with duration more than one human life, where all other means do not exist. Should we say that all current science is just a temporary (relatively non-important and always partially erroneous) extension of primary religion? Science is always pretends that it is in search for only true knowledge and all the rest, erroneous and rejected, has no importance. Due to this reason, when somebody with scientific thought-style sees something not very precise among religious statements, this person is happy to say: "Wrong!" Contrary to this, religious thought-style does not imply that all statements those are looking

correct during this century are better (are more useful or are better entities to comprise the subject of thought) than the ones from previous centuries those are looking not so precise today. Just because two centuries later our current biological views will be looking even more ridiculous than medieval medicine is looking today. Any attempt to understand nature (or universe) is important just because it was done, not because it is looking true and not false today – that's religious approach to reality.

Supplementary Methods

Guinea pig experiment. Outbred short-haired multicoloured guinea pigs (*Cavia porcellus*) were used. Multicoloured female was obtained from Elm Hill Labs (7 Kidder Rd., Chelmsford, MA 01824; www.elmhilllabs.com) and it was bred with short-haired multicoloured male with contrasting whorl on its head (so-called "American crested"), obtained from Petland Discounts #17 (439 Tarrytown Rd., White Plains, NY 10607). Two females and two males were born 2011-09-16. One female from this litter demonstrated low water consumption being an adult.

We had cages "RB100" (100 × 54 × 44.5 cm) and Super Pet "My First Home Chinchilla Cage Kit" (76 × 45.5 × 76.5 cm; a 2-shelf cage, each shelf 44 × 25 cm, placed at 26 cm and 44 cm from the floor in the opposite parts and connected consequently by two ramps 42.5 × 12 cm each). Bottles 500 ml from LM Animal Farms were refilled daily and their weight was measured at 11:00 PM using electronic scale KS/B-2000 (Max: 2000 g, d = 0.1 g). Pine bedding "PetsPick" and bowls with standard guinea pig food were always in cages. Fresh grass was supplied daily, when available. During snow periods animals received "Kaytee Timothy Hay Ultra" and apples. We kept 1-2 adult animals per cage under normal day-light cycle. Each adult animal had its own plastic house "Super Pet Big Igloo" (D = 24.5 cm (lower), d = 19 cm (upper), H = 16 cm (ext.), h = 13.5 cm (int.); entrance tunnel: L = 6 cm, H = 11.5 cm, W = 10 cm).

Above-mentioned female with low adult water consumption was crossed with normal male (her littermate), and from this cross a female with high adult water consumption was obtained, born 2012-03-09. Further comments about animal behaviour can be found in the article[14].

Morphine experiment. Male Wistar rats, 42-day-old initially (P42; body weight 197 ± 20 g, mean ± SD), housed in groups 5-10 under normal day-light cycle, were injected intraperitoneally (i.p.) with morphine during 38 days. The first 7 days – twice daily (morning-evening, 8 hr between, mg/kg): 5-10, 15-15, 20-20, 25-30, 35-40, 45-50, 55-60 (10 mg/ml in 0.9% NaCl). Next day – 60 mg/kg in the morning and 6 hr later – injected i.p. with 2 mg/kg of naloxone (2 mg/ml) to induce early in life naloxone-precipitated morphine withdrawal. Next day – injected with morphine 60 mg/kg. The rest 29 days – injected with morphine 60 mg/kg twice daily Monday-Friday, and 60 mg/kg daily Saturday-Sunday. Control males were left undisturbed.

During the last 5 days of morphine treatment P males were housed individually with drug-naive 75-day-old nulliparous Wistar females. To have F_1-2 (F_1, second brood), P males at the age of 175 days (*i.e.* 95 days of withdrawal) were housed individually with familiar females. To have F_2, F_1-2 males at the age of 85 days were bred individually with F_1-2 females (incross, but without inbreeding).

P, F_1, F_2 animals were tested in tail-withdrawal test at the age of 60-95 days. The distal part of the tail of a lightly restrained animal was dipped into circulating water thermostatically controlled at 56 ± 0.2°C. Latency to respond to the heat stimulus, by a vigorous flexion of the tail, was measured to the nearest 0.1 sec, cutoff latency – 15 sec. This measurement was done once one minute before i.p. 10 mg/kg morphine injection (baseline latency) and 15, 30, 45 and 90 min after. F_2 males at the age of 65 days were tested for morphine tolerance development: each animal received 10 mg/kg morphine daily during seven days and it was tested in the above-mentioned tail-withdrawal test at days 1, 2, 3, 5 and 7 (*i.e.* during these days it received morphine in the frame of testing, and during days 4 and 6 – the same 10 mg/kg morphine without testing).

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