Hello, class! Today we will concentrate on positive and negative properties of mutations. Indeed, mutations are ambivalent. They can cause many diseases, yet at the same time they drive the evolution. During last ten million years they created a human being from a chimpanzee-like ape.

SLIDE1. Last month I introduced you to a very interesting book written by Dr. Jonh Sanford in 2005.

This book brings up many vague issues and as yet unresolved intricacies in modern population genetics.  The book claims that under modern genetic conceptions and rules, mankind cannot withstand the current rate of mutations in the human genome.

Dr. Sanford states that these mutations should lead to rapid degradation of the genome, in turn leading to degradation of the mankind. Since this is not observed, he claims that the Darwinian theory of evolution is incorrect.   Instead, he proposes the Intelligent Design solution.

SLIDE2. I very much respect Dr. Sanford’s ideas and conclusions. I think that he is an extremely clever scientist, who has enormous courage to present his real thoughts.

This slide demonstrates the impressive credentials of Dr. Sanford.

I agree with all of his scientific conclusions about problems in population genetics except the last statement about Intelligent Design.

I am not against Religion, yet I simply do not believe that God controls all 10 trillion cells of a body of each human individual. However, this topic is totally outside the scope of this course and my main scientific interests.

SLIDE 3. Today I will present alternative SCIENTIFIC explanations to major problems Dr. Sanford raised in his book.

Last month I demonstrated to you a fragment of Sanford’s lecture available on U-tube via this link at the top of this page. And here is a slide from this lecture with very important statements on the human genetics.

I 100% agree with these four scientific facts:

Indeed every human individual has more than one hundred new genomic mutations.

2-3% percent of newborns have genetic diseases. Currently, more than 6000 human monogenic genetic disorders have been described.

However, I am not satisfied with the clarity of the second statement that is concentrated only on bad mutations. I hold a more balanced view that “there are thousands of bad and good mutations” in each individual.

And finally, I disagree with statement number 5, that mutations lead us to degeneration.

SLIDE4. This is my vision of the human evolution. Mutations inevitably lead human beings to change in the future. We are doomed to change in time, yet this change is not always bad. However, in ten million years the appearance of humans certainly should change significantly. The magnitude of this future change may be comparable to the change during the last 10 million years when humans evolved from chimp-like creatures to our modern appearance.

SLIDE 5. Here is your special assignment from last month related to Sanford’s book. For the completion of this task I promised to you extra-credits and/or an excellent grade for your next exam.

This slide demonstrates the most popular scheme for the origin of new genes, which you can find in a majority of textbooks about genes and genome evolution.

This theory claims that a new gene originates via a process of gene duplication followed by mutations that sometimes cause an appearance of a new function.

Gene duplication occurs pretty frequently in all organisms from tiny bacteria to humans. It is a stochastic process and all types of genes have a good chance to be duplicated during evolution.

This scheme illustrates a duplication of a gene with a name A. After its duplication there are two identical copies of this gene A1 and A2. One copy of this gene preserves the same original function of the gene A and on this slide it is A2 copy, while another copy is free from its duty and can lose its original function and rapidly accumulate mutations shown as red stars on the slide. All these new mutations might lead to the origin of new function and new gene.

I absolutely agree with Dr. Sanford, that this scheme does not work.

However, there are alternative theories on the origin of new genes. Your special homework assignment was to find out alternative theories for origin of new genes.

SLIDE 6. Here is a funny cartoon that criticizes the discussed scheme of the origin of new genes. I took it from the Internet publication about the Sanford’s book. The link to this site is shown on the left. It is obvious that random mutations cannot create a new complex function. However, it is not a problem for them to destroy any gene in any organism.

SLIDE 7. I guess that all of us agree that the common theory of gene origin due to gene duplication followed by mutations and acquisition of new function DOES NOT WORK. However, there should be alternative theories on this very important biological question. During the first part of my lecture we will discuss these alternatives.

SLIDE 8.

There are a lot of ambiguities in Biology. Almost every biological topic has some controversies and contrasting interpretations. Last weeks we saw well-know examples of such controversies. For instance, during my lecture 5 we discussed alternative explanations on the origin of codon bias. While in the lecture 6 I introduced you to the long-standing debate on the origin of introns. It is a 25-years old battle between early-or-late intron hypotheses. Today we will touch another disputable issue on the genome evolution – I am talking about Neutralism versus Selectionism views.

Anyway, my message is that there are numerous controversies in biology, even for a primitive question like what was the first the Chicken or the Egg.

Obviously, there must be alternative explanations on the origin of novel genes. We will concentrate on this issue in a moment. In addition, we will talk about how bad mutations are for genes and proteins and how often do they bring benefits.

SLIDE 9. We are hit by a tsunami of information in modern Biology. It is impossible to find, read, and appreciate all pieces of published data. Even very respectful professionals may not know some essential things in the field they are working in. Nowadays, scientists frequently do not discover something new but reinvent the wheel.

SLIDE 10. Here is a summary of what you found during your special assignment while hunting for alternative hypotheses for the origin of novel genes.

Three students successfully accomplished this task. Hence I gave them “A+”. They can keep this grade as an extra credit, or skip the exam next week.

All in all, these three students listed seven scenarios describing the birth of new genes. They are the following:

All these scenarios are based on real characterized and verified examples. Hence all of them took place in some organisms during evolution. We will examine some of these schemes next week. HOWEVER, this list is not completed! Today I will talk about the eighth scheme, which is missing here.

I performed this experiment with a strong grading incentive to demonstrate to you that sometimes it is very hard to find an existing biological theory, which has been known for many years. In fact, all students from my laboratory also were unable to uncover this eighth scenario.

SLIDE 11. It is absolutely unsurprising to me that you have not found one very important concept on the origin of novel genes, on which I will focus on in today’s lecture. It is known under several names including, so-called Sharing Genes. And here is the picture of the book published in 2007 by Joram Piatigorsky that details this Sharing Genes theory.

VIDEO. Here is this book. It is comprised of 320 pages and includes many colorful pictures and schemes. The sole disadvantage of the book -- it is not cheap. I paid more than $60 for it. This book received many positive reviews and here is one of them… From Stanford University written by Dr. Fernald:

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SLIDE 12. This slide exemplifies another review on this book, which you can get from Amazon.com web-pages.

SLIDE 13. I would like to stress, that Sharing Genes concept is not new. It has been known for a number of years under several names. One of the popular names of this concept is Moonlight Proteins. Here are references on two good reviews on Moonlight Proteins from 1999 and 2003. I put PDFs of these articles into the folder for this lecture.

Here are two other alternative names for Moonlight Proteins -- Hijacking Proteins and Co-option Proteins.

In his book, Joram Piatigorsky provides an interesting history of this theory. He references these earliest publications by Orgel and Jensen. You see that ideas on Sharing Genes appeared as early as mid 70ies of the last century.

SLIDE 14. This is an outline of the Gene Sharing concept for the origin of novel genes. The theory is based on the notion that a single protein may have several different functions. This scheme illustrates the origin of a new gene with a new function B. Originally, a primordial gene had coded a protein with a sole function A. The gene may have existing for millions of years. Then, at some time point, a new function B emerged in the same gene due to mutation process. After this event the protein coded by the gene became a Moonlighting protein that performed two different jobs at the same time. Such events are not rare in the course of evolution and a gene could present a moonlighting protein for millions of years. Then at another point in time during evolution, the gene on this scheme underwent duplication process and two identical copies of it appeared. Initially both of the copies coded the same Moonlighting protein with functions A and B. However, mutations, that happen constantly during evolution, could destroy the function A in one gene copy without any problem to an organism until the same function is active in another gene copy. Vise versa, the function B could be soon destroyed by mutations in the second copy without any harm to the organism, until this function is preserved intact in the first copy.

This scenario might be very beneficial to an organism, because it allows separating functions A and B and have them associated with separate protein molecules. Now the expression of functions A and B is not linked to each other. This separation provides a new level of flexibility in expression regulation across different tissues and in response to various stimuli.

SLIDE 15. I would like to demonstrate some examples of gene sharing. And here is the famous one, which I took from the Joram Piatigorsky’s book. Particularly, this is a fragment from the table published on page 62. For a number of years Dr. Piatigorsky investigated crystalline proteins – the major component of eye lenses in mammals and vertebrates. Inside a lens these proteins provide the structural stability for this tissue and at the same time the transparency for a light passing through the lens. Interestingly, the same proteins are expressed in other tissues where they serve completely different purposes. A majority of them are enzymes. Here I listed only four of moonlighting functions of crystalline proteins while the entire table contains 12 different functions.

This example is not a rare exception; in fact, a large portion of proteins possess moonlighting properties.

SLIDE 16. This slide compares two theories for the origin of novel gene. At the top there is a common view, presented in many textbooks, which was criticized by Dr. Sanford. While at the bottom there is a Gene Sharing scheme. On my view, the latter theory is much more realistic and elegant. It allows a gradual evolution of a new function B in the same gene bearing the original function A. There is no rush for the evolution of a new function B under this scenario. It can take millions of years for random mutations to generate something new and valuable. Moreover, there is plenty of room for the creation of additional moonlighting functionality, which is illuminated on the next slide.

SLIDE 17. Here is a sketch for a protein. Proteins are macromolecules that are usually composed from hundreds of amino acid residues. Yet, their functional active sites are reasonably small. Here, an arrow demonstrates a cavity on the protein surface that represents a typical active site. HOWEVER, there is a lot of room on the rest of the protein surface to evolve a new function. Look, here is another good cavity to fit a small molecule among thousands of different kinds existed in each cell. Here is another decent cavity to start evolution of a new function. And so on. Here is a molecular finger with a good potential to interact with some other macromolecules like proteins or nucleic acids. A constant flow of mutations permanently changes shape of the surface of each protein during millions of years. UNSURPRISINGLY, many cavities and protrusions on the surface of proteins besides the well-recognized active sites are also functional. They may perform supportive regulatory roles or completely unrelated moonlighting functions.

SLIDE 18. This is a snapshot from a video about hemoglobin molecules which I downloaded from the educational web-pages of HU Medical School. And at the top of thuis slide is the link to this great resource. I would like to acknowledge the author of this web site, Janet Iwasa, who permitted using these data for educational purposes. I will show you these videos in a moment, but at this point I would like to concentrate your attention on the proportional size of the hemoglobin protein, shown in blue and the size of oxygen molecules shown in red. The latter are so tiny compared to the protein, thus they are barely seen. Therefore, I should help you to identify four oxygen molecules in this picture by these arrows. Actually, oxygen binds to the small co-factor, the heme group, presented in this picture in a ball-and-stick format. The message of this illustration is that an active site comprises only a few percentages of entire protein.

SLIDE 19. For several decades, there was a simple and convincing explanation for the excessive size of the proteins. They should withstand the thermal motion and collisions with all the molecules from their vicinity. Here is a nice video-demonstration for the thermal motion of proteins that I found in the Internet. I found a great web site about macromolecular modeling created by the Theoretical and Computational Biophysics Group from the University of Illinois at Urbana-Champaign. Here is a link to this web page.

However, since I have not received an explicit permission from this group for public demonstration of their videos, I will show you a 10 second fragment from the U-tube movie.

You see, everything is shaking in the micro world. Therefore to be more stable there, you need to be bigger and bigger.

Here are two more movies on the same subject. The second one lasts several minutes and I recommend you to watch it alone. But I will show you the first one.

SLIDE 20. Another important characteristic of proteins is their ability to change conformations. Let’s examine this characteristic using one of the best studied molecules – hemoglobin. Again, I appreciate the public policy of Harvard University and Janet Iwasa for allowing me to demonstrate their video during this lecture.

Mammalian hemoglobins are hetero-mers composed from two beta-like globin chains and two alpha-like globin chains. In adults they are represented by beta-globins and alpha-globins shown on this picture.

Hemoglobin transports oxygen from lungs into other tissues. In addition it transports carbon dioxide back from tissues into the lungs. Also, it transports NO - nitric oxide gas. Therefore it is a multifunctional protein, and different gas molecules bind to different parts of hemoglobin. Besides its main function in erythrocytes, hemoglobin is expressed in several other cell types including specific neurons, macrophages and some other cell types where it performs different moonlighting functions. All these moonlighting properties are well described in Wikipedia. However, if you screen thousands of scientific papers about hemoglobin, you may find additional hemoglobin properties not specified in Wikipedia and in this presentation. All in all, this protein has at least five other moonlighting functions besides transportation of oxygen.

Now let’s watch the movie (intro\_TtoRzoom). Hemoglobin exists at two major conformations – so called T-form and R-form. And here is the transition between T and R states. These two states have different binding capacity to oxygen. A heme group contacts with the neighboring histidine residue and during TR transition the movement of this particular histidine changes the heme shape and, as a consequence, its binding capacity to oxygen.

This segment of the video (binding\_oxygen) demonstrates that at T-conformation the hemoglobin is reluctant to attach oxygen. However, binding of the first oxygen molecule to the deoxy-hemoglobin induces the T to R-state transition and facilitates binding other oxygen molecules with the three other active sites.

Now lets watch the entire video (intro3\_hemoglobin)

Finally, the last segment of the video demonstrates that a particular small molecule also has specificity for binding to hemoglobin (BPGbinding.mov). This molecule is 2,3-Bisphosphoglycerate or 2,3-BPG. It is abundant in erythrocytes where it binds with greater affinity to deoxygenated hemoglobin, while binding to hemoglobin BPG decreases its affinity for oxygen. Thus, PPG stimulates the hemoglobin to release oxygen near tissues that need it most.

VIDEO. The effective function of hemoglobin is achieved by the ability of this protein to change its conformation. Hemoglobin performs many functions simultaneously and nobody tells it what to do in the different tissues. In the lungs there is the highest concentration of oxygen and the lowest of carbon dioxide. Therefore, the pH of blood in the lungs reaches its highest level. This high pH stimulates the transition of hemoglobin from T to R conformation and, as a consequence, the release of CO2 and binding O2. After passing the lungs, erythrocytes are delivered to different organs such as muscles, kidneys, etc., where the level of CO2 is much higher. This carbon dioxide reacts with water to give carbonic acid. This reaction reduces the pH of plasma considerably. Low pH stimulates a reverse conformational transition of hemoglobin and the release of oxygen and the uptake of CO2. Therefore, the hemoglobin movement is crucial for its function.

SLIDE 21. Here is another excellent educational resource on Wikipedia pages about hemoglobin structure and functioning. I downloaded this movie about T – R hemoglobin transitions from the web-site with this URL. Isn’t it a great demonstration how the moving protein parts change the affinity of this molecule to the oxygen? Also please see how the T-R transition alters the local cavities and protrusions all around the protein surface.

SLIDE 22. Conformational changes are extremely important to a number of proteins with various functions. I will give you three more examples on this important topic.

This picture I took from another superb educational resource we already worked with during last month. These are Protein Data Bank educational pages. Particularly this is their section “The molecule of the month”. I highly recommend you to visit these sites.

This particular link guides you to the web-pages about glycolytic enzymes. It describes all ten enzymes in this pathway starting from the first one, hexokinase, which you see on this picture. Hexokinase transfers a phosphate from ATP to glucose, forming glucose-6-phosphate molecules. It exists in two conformations with an open cavity, shown on the left with the arrow, and with a closed one shown on the right. When a glucose binds to this cavity the molecule closes its jaw to perform the enzymatic reaction. This movement is absolutely crucial for the function. All the details are provided on this web site.

SLIDE 23. The third enzyme in the glycolytic cascade is Phosphofructokinase illustrated on this slide. Indeed you need to read all these PDB pages yourself. Below is a small fragment of the text about Phosphofructokinase.

Phosphofructokinase is like a miniature molecular computer that senses the levels of different molecules and decides if the time is right for breakdown of sugar. Many different molecules associated with glycolytic cascade bind to different places on the surface of phosphofructokinase. They regulate conformational transitions of the enzyme and turn on and off its activity.

Here is an interesting statement from this Internet source: “Phosphfructokinase is a mechanical computer, with moving parts”. In a nutshell, many parts of a protein are involved frequently in different interactions and activities. So, multi-functionality and moonlighting is a common property and not a rare exception.

SLIDE 24. Here is my last example of protein movement. This is a completely different type of molecule – a transcription factor that interacts with DNA and regulates the gene expression. Particularly, this is a bacterial Lac-repressor.

First of all, I must acknowledge the authors of this movie. I took it from another superb Internet educational source – Proteopedia. The demonstrations that we will see in a moment were originally prepared by Eric Martz and co-authors. And below is the link to the web site containing all these data.

The two strands of DNA are shown here in yellow and orange, while the protein is shown in white and red. The red segments present alpha-helices.

This protein binds to DNA non-specifically at any site and glides along it until it reaches its sequence-specific binding site. And here we see exactly this moment. At this place Lac-repressor changes its conformation. It bends DNA and widens its minor groove. Simultaneously, the protein undergoes conformational changes. Its middle stretch of amino acids transforms into additional alpha-helix structure and becomes inserted into the widened minor groove. The change of protein shape is crucial for the molecule function. Importantly, Lac-repressor also can bind lactose, which changes its conformation to an inactive form that cannot interact with DNA and as a consequence, cannot repress the production of the enzymes involved in the metabolism of the lactose. Thus, the enzymes needed to utilize lactose are made only when lactose is available.

Let’s open this Internet page and examine the movement of protein parts. This web site has interactive properties. You can click on green text segments to change the illustrations.

SLIDE 25.

Here are important conclusions. Protein ability to alter conformations is essential for its function.

Proteins should preserve their different shapes and precisely regulate transitions from one conformation into another inside thermal motion environment.

It is another reason why proteins are so big compared to the dimension of their active sites.

SLIDE 26. Now we have reached the second part of our discussion. It is time to consider how really bad mutations are for their host organisms.

SLIDE 27. The proteins are very flexible because they utilize predominantly weak forces for their folding. Different types of these interactions are listed here. Hydrogen bonds are among the strongest ones. Then there are several kinds of van Der Waals interactions; interactions between positively and negatively charged ions and hydrophobic interactions in aquatic environment. Covalent bonds between amino acid residues are very rare inside the cell. Occasionally, they are presented by disulfide cysteine bonds.

Therefore, a single mutation frequently causes a small effect by creation, modification, or disruption of a weak binding site.

SLIDE 28. Here is the Genetic Table downloaded from the Wikipedia. Major amino acid properties are shown in color. Hydrophobic residues are yellow, hydrophilic -- are green, positively charged residues existing under physiological conditions are shown in blue, and negatively charged are pink.

Hydrophobic interactions occur between residues shown in yellow. Their positions in the table are non-random. As you can see, the entire first column of the table is yellow. Frequently, mutations change one hydrophobic residue to another one. For instance, in the first column any mutation in the first or the third codon position may only replace one hydrophobic residue to another one. Among various types of mutations, transitions are twice frequent than transvertions. Therefore, substitutions frequently occur between Leucine and Proline and also between Alanine and Valine due to transitions in the second codon positions.

SLIDE 29. Hydrophobic amino acid residues of a protein are clustered in space. Usually they comprise an inner core of globular proteins. Let’s examine these characteristics using PDB J-mol web resource. Here is an already familiar hexokinase.

Let’s click on this 2yhx identifier and study the structure of this protein using interactive Internet facilities. We need to click on Jmol view and then allow using our local computer.

Let’s switch to a Ball and Stick view inside the first window and to Hydrophobicity inside the second window. Then I like to activate the rotation option. And here it is. Hydorphobic AA are shown in red and hydrophilic in blue. This is a typical picture: hydrophobic residues are in space pockets in the inner part of the protein. They cannot occupy large areas on the surface, because it will cause aggregation of the protein molecules with each other in aquatic solution. These non-polar amino acid residues do not significantly attract to each other, but rather stay in a whole group allowing H2O molecules to form more dipole-dipole interactions between themselves according to molecular thermodynamics. This is like sheep in a herd – they are always close to each other but there is no strong physical force that keeps them in such a cluster. Hence, a mutation of one hydrophobic residue to another one often is neutral.

Moreover, even when a mutation creates an unfavorable contact, for example, creating a new ion in a close proximity to another ion with the same electric charge, these unfavorable residues may be move noticeably apart from each other due to significant flexibility of amino acid residues in a polypeptide chain.

SLIDE 30. We have already considered the same effect for nucleic acids at my first lecture in this course. This slide I demonstrated to you last month. It is a segment of ribosomal RNA molecule – so called Sarcin/ricin stem-loop motif – an evolutionary conserved domain that exists in both eukaryotes and prokaryotes. Here is a stem formed predominantly by non-Watson-Crick base pairs. And here in pink is one extra nucleotide that bulges on one of RNA chains.

SLIDE 31. Here it is on the next slide. This is an extra G on the left chain. It is so-called bulged nucleotide inside the stem, where all other nucleotides are paired with their counterparts. At first glance, we are likely to conclude that this unpaired G should considerably destabilize the stem. However, let’s return to the structure and see what’s going on in reality. Due to the flexibility of RNA molecule, this unpaired G twists considerably the molecule backbone and turns in such a way that it establishes non-WC base pairing with another base here and also forms stacking interaction with the nucleotide above it.

After all, maybe it is not so bad for this stem to have this bulged nucleotide if it can fix the situation by adjusting its position relative to the rest of nucleotides and form new connections.

By the way, this sarcin/ricin domain is very similar in bacteria and eukaryotes. Here is the secondary structure of the motif from an archaea branch of prokaryotes, while this is an identifier of the same motif for the rat 28S ribosomal RNA in the Protein Data Bank. I am going to show its structure to you once again.

PDB DEMONSTRATION

VIDEO. Similar to nucleic acids, proteins are also very flexible macromolecules. They also can shake their structure and adjust to a mutation by rotating and bending their neighboring amino acids. Thus, a considerable portion of mutations should be relatively neutral to the main protein functions. In one of the latest chapters of his book, Joram Piatigorski specifically considers alternation of protein structures and refers to recent publications about very fast and constant transitions between several local conformations.

SLIDE 32. In addition to genomic mutations, there is another important source of mutations inside proteins. I am talking about translational errors. An estimated rate of translational errors is about one misreading amino acid per 5 thousand codons. This rate is very high. However, there is a considerable discrepancy in estimation of the rate of translational errors in the scientific literature. Anyway, let’s consider our canonical example – the human adult hemoglobin A is composed of two beta-globin chains each of 146 residues and two alpha chains of 141 residues. So, altogether this molecule consists of 574 amino acids. Therefore about 11% of these molecules should be mutant due to translational errors, even when beta and alpha globin genomic coding sequences are perfect! Moreover, the hemoglobin is a reasonably small molecule. A considerable portion of eukaryotic proteins consists of more than a thousand residues. Rememeber, the longest protein chain in humans belong to titin. The coding sequence of its gene is comprised by 26,000 codons! Therefore, a large portion of human proteins should be mutant only due to translational errors.

My conjecture is that proteins are so long compared to their relatively small active centers due to several reasons discussed above and also presumably to withstand translational errors. Indeed, a substantial protein safety factor in the form of exta-length may provide additional stability against all kinds of mutations.

SLIDE 33. Translational errors are a controversial topic. Different molecules have different translational mutations. These errors are unique to single protein molecules. Presently there is no experimental technique to study amino acid sequence in individual molecules. The situation is much better in respect to nucleic acids. In this case using PCR chain reaction we are able to amplify a single DNA chain and thus, investigate the difference between individual molecules. Predictably, in the literature there is a discordance of estimation of the rate of translational errors. Here I present a randomly picked paper showing high frequency of translational misreading errors in bacteria.

SLIDE 34. I will not go into details of the debate about the rate of translational errors. This will be your task. I decided to give this problem as your take-home exam. You need to write a minimum of 3 pages and describe the best experiment you can think of or find in the literature for the estimation of the rate of translational errors.

SLIDE 34.

I would like to finish this part of my talk about Sharing Genes with this fascinating example of the human keratoepithelin. **Keratoepithelin** is a primary component of cornea composing nearly 20% of its protein mass. It performs a structural function in organization of this tissue.

The same protein is also found in blood and has a different name (big-H3) and, apparently, differnet function.

This protein is also known as Transforming growth factor, beta-induced, 68kD (TGFBI, other names include the following: BIGH3; CDB1; CDG2; CDGG1; CSD; CSD1; CSD2; CSD3; EBMD; LCD1.

The homolog of keratoepithelin in Drosophila has 25% of sequence identity with the human counterpart. In fuit fly it is known as midline fasciclin and it plays multiple developmental roles including axonogenesis.

The protein has homologs in yeast and among bacteria that obviously serves other roles than in human and fly.

This protein has several duplicates in mammalian genomes. Apparently, evolution of this gene is in favor of Gene Sharing theory.

SLIDE 35. Here are my conclusions on mutations. Mutations are ambivalent. They have dark and bright sides of their effects on the host organism. Here negative attributes of mutations are shown in red while positive in green. On one side, mutations may disrupt a gene function and, thus, create a trouble for their host. On the other side, they gradually change a phenotype and drive the evolution.

Importantly, a majority of mutations are relatively neutral and each of those does not have an evident effect on the organism.

SLIDE 45.

Indeed, if S-values for genomic mutations are distributed according to this popular curve, then mankind should go down the degradation spiral quickly and inevitably.

HOWEVER, this is a pure imaginable curve without strong experimental support. It is absolutely impossible to measure the S-value for near-neutral mutations. There is no strong argument why this particular distribution must be correct. It is one of multiple delusions that are common in our life.