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FINE-TUNING ARGUMENT IN HUMAN BEING FROM THE PERSPECTIVE OF MOLECULAR BIOLOGY

Selcen ÇELİK UZUNER*

ABSTRACT

Fine tuning argument has been of interest in physics and philosophy to explain the existence of the universe which is best fit for life; however, it has not been extensively applied to biological sciences in particular molecular biology. Molecular biology is different from physics and mathematics as it has stochastic events and limited laws. Biological sciences should be revisited for constants and laws. Though, the systematic events in the cells bring on the possibility of fine-tuning in molecular biology. Cells systematically perform many molecular mechanisms at molecule, gene, and genome levels. This work focuses on the fine-tuning argument in the cell and the genome and suggests four parameters of excellences (fundamental contexts) for fine-tuning including 1) position, 2) interaction, 3) amount, and 4) time which occur at molecule, gene, genome and/or organism levels. These fine-tuning contexts are associated with each other and manage life together. Systematic cellular activities suggest that this complexity is managed by fine-tuning in the human's molecular system.

Keywords: *Fine tuning argument, molecular biology, philosophy, randomness, design*

MOLEKÜLER BİYOLOJİ AÇISINDAN İNSANDA HASSAS AYAR ARGÜMANI

ÖZ

Hassas ayar argümanı, yaşama en uygun olan evrenin varlığını açıklamak için fizik ve felsefenin ilgisini çekmiştir; ancak biyolojik bilimlerde, özellikle moleküler biyolojide kapsamlı bir şekilde tartışılmamıştır. Moleküler biyoloji, stokastik olaylara ve sınırlı yasalara sahip olması nedeniyle fizik ve matematikten farklıdır. Sabitler ve yasalar için biyolojik bilimler yeniden gözden geçirilmelidir. Ancak hücrelerdeki sistematik olaylar, moleküler biyolojide hassas ayarlar olma olasılığını da beraberinde getirmektedir. Hücreler molekül, gen ve genom düzeyinde birçok moleküler mekanizmayı sistematik olarak gerçekleştirir. Bu çalışma, hücredeki ve genomdaki hassas ayar argümanına odaklanmakta ve bu hassas ayarlar için molekül, gen, genom ve/veya organizma seviyelerinde meydana gelen 1) konum, 2) etkileşim, 3) miktar ve 4) zaman dahil olmak üzere dört mükemmellik parametresi önermektedir. Bu ayarlar birbiriyle ilişkili olup hayatı birlikte yönetmektedir. Sistematik hücresel aktiviteler, bu karmaşıklığın insanın moleküler sistemindeki hassas ayarlarla yönetildiğine işaret etmektedir.

Anahtar Kelimeler: *Hassas ayar argümanı, moleküler biyoloji, felsefe, rastlantısallık, tasarım*

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* Doç. Dr / Assoc. Prof. Dr. Karadeniz Technical University, Faculty of Science, Department of Molecular Biology and Genetics, Trabzon, TÜRKİYE,
ORCID: 0000-0002-9558-7048, E-posta: selcen.celik@ktu.edu.tr
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Backyard of Fine-Tuning Argument: Randomness or Design?

Explaining our existence is one of main concerns of scientists and philosophers. Humans are always interested in asking how they exist and why. One of the common explanations is "fine-tuning argument" (FTA) which supports the idea that our universe and existence are based on a design. The other explanation is "multiple universe argument" (MUA) (discussed later). Some philosophers and physicists support one of them to explain [1]. However, some discuss that fine tuning does not necessarily need an explanation [2]. Doko claims that no explanation is required because fine tuning itself is not surprising, and only rare events are surprising so that they need an explanation [3]. Rare events are likely random. Çalışkan argues how necessity and randomness are closely related to each other even if they point out different contexts. The smallest units (*i.e.,* atoms or molecules) behave randomly, but when many of them come together, a predictable result emerges. He claims that chance is the basic constructive element of the universe, responsible for both order and disorder, rather than an exceptional situation that disrupts order from time to time and concludes that randomness builds the universe; coincidence is a result of the algorithm [4]. Randomness is discussed as the opposite of design (or intelligent design). Cosmic fine-tuning has been related to a Creator, and randomness is a chaotic phenomenon against fine-tuning argument. Therefore, randomness is closely associated with the debates for the existence of our universe and our living.

Randomness is defined as a relative notion depending on the selection of the set of rules [5]. Randomness theory has varieties including theories of finite and infinite things, and algorithmic randomness based on the explanation of random infinite sequences is applicable to biology and physics [6]. For instance, some mutations are random events with no associative factors proven but some mutations are not random as there are inducible factors mutating DNA such as exposure to genotoxic conditions (UV, chemicals *etc.*). However, it is still random which gene or genes in which cell types will be mutated by these inducible factors. On the other hand, a part of mutations randomly occurs during DNA replication (not by inducing factors) which is defined by "the rate of replication error" (an error per 100 million replication) [7]. A DNA molecule in a human cell is almost 2 meter long.

[1] Tegmark, 'Parallel Universes'.
[2] Colyvan, Garfield, and Priest, 'Problems with the Argument from Fine Tuning'; Landsman, 'The Fine-Tuning Argument: Exploring the Improbability of Our Existence'.
[3] Doko, 'Does Fine-Tuning Need an Explanation?'
[4] Çalışkan, *Rastlanti Bilim ve Felsefenin Ortasi*.
[5] Terwijn, 'The Mathematical Foundations of Randomness'.
[6] Terwijn.
[7] Pray, 'Errors in DNA Replication'.

Therefore, it is not unexpected that replicating this long molecule at once (even if performed by using many replication forks) has some ontological error rate.

The molecular events within the cells occur based on the possibilities of various mechanical systems of living things. I will discuss how these intracellular mechanisms arise within the scope of the fine-tuning argument. These possibilities determine certain limits in terms of the order of living things rather than being spectacular and precise like the laws in physics. Therefore, it is concluded that the cellular events do not happen by coincidence or chance but by the possible pathways of living matters regarding intra- and extra-cellular conditions.

Revisiting "Randomness"

An important concern is that the intuition of randomness can be faulty by the nature of scientific methods. There are two factors affecting randomness 1) publication bias and 2) confirmation bias [8]. Publication bias is because researchers tend to publish only positive results which support their hypotheses. Negative results are not such of interest in science publishers but still valuable for science itself. The probability that repeats of an experiment gives the same outcome is very low and almost never happens, so results of repeats always have variance. In addition, the results (characterised by averages of repeats) represent the feature of a particular sample. Statistics is the perfect discipline to interpret data regarding probabilities and randomness. Therefore, statistical analyses conclude the results are significantly different or not. This significance is then concluded as "an estimated general pattern" for a fact. In a specific example for molecular biology, the best way to understand what happens in the cells is to do single cell analyses using third generation sequencing methods. But currently, these methods are highly expensive. Thus, the general approach in experimental biology is to work with cell populations rather than separating and analysing cells individually. Therefore, this general method gives us 'a general' or 'an average pattern' for the response of cells. To deal with these obstacles, having intra- and inter-repeats of an experiment seems applicable. Independent experimental repeats (inter-repeats) along with repeat groups in an experiment (intra-repeats) will give more reliable outcomes. But this should be noted that a natural variation already exists in living systems which indicate the differences between individuals in addition to experimental variety.

Confirmation bias is about the different ways/methods to test a hypothesis which cannot conclude the similar results [9]. Each method has advantages and disadvantages, and a limitation of a method can be overcome by another method so

[8] Goeman, 'Randomness and the Games of Science'.
[9] Goeman.

there is no perfect technique to perform a wet lab. New technological and methodological discoveries are an important aspect to rethink about the current scientific findings. In DNA research, sequencing technologies are the gold-standard methods to achieve base patterns of a DNA molecule. DNA is not only sequenced for base compositions but also a variety of epigenetic modifications on DNA. Revised methodologies are on demand with increases in epigenetic information. These therefore suggest that today's finding may not reflect the truth at all, and all the findings need to be revisited and re-concluded by new technologies. The revisiting of current knowledge can change the interpretation of false positive or false negative results. Goeman suggests that "*the only way to avoid false positives completely is never to publish, and the only way to avoid false negatives completely is always to publish, regardless of evidence*" [10]. But it appears important that unpublished false positive results can underestimate the outcome. Some data may be false positive or false negative with the current methods, but new methods may clarify whether these are false negative or positive so that revising previously wrong conclusions.

Fine-Tuning Argument vs Multiple Universes Argument

The fine-tuning is associated with the existence of a Creator and explained by "Argument of Design". But Landsman suggests that fine tuning itself is not a sufficient basis for design argument because *"it is the combination with an assumption to the effect that life is somehow singled out, preferred or special"*. The universe is not fine-tuned for life, but life is fine-tuned for the universe [11]. Colyvan *et al.* also discussed the methodological problems for concluding the improbability of FTA so that no explanation for FTA is required [12].

The opposite argument is the multiple universe argument (MUA). This stands for the idea that our universe is the only universe suitable for life within multiple universes, and this is the reason why only our universe exists but no other universes. MUA is the most preferred explanation about our existence by non-theists. But even if the multiverse argument is true this does not prove the absence of a Creator. A creator, if he/she exists, should be able to create multiverses as well. This is totally related to how we define the concept of a "Creator". This is also considerably a combined approach of fine tuning in the multiverse hypothesis that our universe is fit for life as it has fine-tuning but other universes do not. This may be the answer to Manson asking, "Why is this universe fit for life?" [13]. Thus, Friederich discusses the

[10] Goeman.
[11] Landsman, 'The Fine-Tuning Argument: Exploring the Improbability of Our Existence'.
[12] Colyvan, Garfield, and Priest, 'Problems with the Argument from Fine Tuning'.
[13] Manson, 'The Fine-Tuning Argument'.

possible types of FTA for the Multiverse [14]. Nevertheless, how can we make sure that there are no other universes with life right now? There may be other universes with another concept of fine-tuning that we do not know with the current knowledge.

Fine tuning can be classified into three groups: 1) the fine-tuning of the laws of nature (*i.e.,* electromagnetic force and strong nuclear force), 2) the fine-tuning of the basic physical constants (*i.e.,* the cosmological constant and the dimensionality of the universe) and 3) the fine-tuning of the initial conditions of the universe (*i.e.,* the amplitude of primordial fluctuations and initial entropy of the universe) [15]. FTA is generally based on physical formulations and calculations. Group 1 is more likely related to molecular biology-related disciplines. But the definition of "law" should be revisited for molecular biology.

Does Fine-Tuning Exist in (Molecular) Biology?

Fine-tuning in molecular biology remains elusive whereas fine-tuning in physical sciences has been comprehensively discussed. One of the main reasons why biological sciences are hard to be considered for FTA is that living systems cannot be predictable to some extent compared to non-living systems. This is because mathematics is applicable in the context of precise calculations to define certain rules. For instance, mass of the proton (M_p), mass of the neutron (M_n), speed of the light (c) and the Newtonian gravitational constant (G) are the calculated numerical values in physics [16]. FTA concludes that there would be no universe suitable for life if one of these values varies whereas others remain fixed. But in molecular biology there are nominal parameters rather than actual values to understand and define how organisms live. I may suggest "parameters* of excellence" for the specific use of fine tuning in molecular biology.

The other reason is that biology is a science with a limited number of laws. Biological rules cannot be easily definable due to the nature of living systems but there are some laws in molecular biology and genetics. The most famous one is Mendelian Rules for genetic inheritance. Gregor Johann Mendel (1822 – 1884) is the father of genetics as his studies have been still taught in classical genetic lectures at all the universities around the world. Even if there were no molecular techniques (DNA was not known either) he was successful in concluding fundamental principles of inheritance between generations. The scientific background of his

[14] Friederich, 'A New Fine-Tuning Argument for the Multiverse'.
[15] Doko, 'Does Fine-Tuning Need an Explanation?'
[16] Manson, 'The Fine-Tuning Argument'.
*Parameters suggested in this study do not represent numerical values at all. Amount and time are measurable but other fine-tuning contexts (position and interaction) not. Thus, I use the term "parameter" in isolation from the sense of measurability.

success is based on "selection of explainable observations by his eyes" and "selection of the organism (peas) that can be easily observed for phenotypic changes". Mendel might have selected the phenotypic samples that he could explain, because today we know that there are many phenotypes which cannot be explained by classical Mendelian rules, such as codominance and the lack of dominance as well as epigenetic-mediated phenotypic differences. Mendel might have seen some samples that could not be explained by the current scientific background at that time. Therefore, we can assume that Mendel published his observations with the specifically selected cases. This may be considered by the relation to publication biases stated by Goeman (2016). Dhar and Giulioli discussed that Mendel's success is related to his approach for finding "constant(s)" in the scope of inheritance as he mentioned the word "*constant*" 69 times in his paper [17]. Thanks to Mendel for publishing his data anyway, otherwise we would have more way to go.

In addition to Mendelian Rules/Laws, there is a concept named "central dogma" in molecular biology. Central dogma refers to genetic code transfer from DNA to RNA and from RNA to protein. This explains how DNA is transcribed to RNA, and how RNA is translated to proteins. There are still no biological constants and formulas but only genetic probabilities (defined by Mendel) and molecular potentials (by central dogma). Because not all RNAs are translated to proteins so that they are called 'non-coding RNA'. It means that central dogma presents the optional translation which suggests "central dogma" cannot be precisely "a law". Trevors and Saier Jr concluded three laws of biology: all living organisms 1) abide by the rules of thermodynamics, 2) have enclosed cells with a membrane, and 3) evolved in an evolutionary process [18]. The laws in molecular biology can be extended further, and it would be nice that biologists may conclude rules/laws in detail. Currently, there has been no consensus about biological laws. Dhar and Giuliani (2010) offer a bio-periodic table consisting of "(1) constants at the same level, (2) among constants at different levels and (3) among constants and variables at the same and different levels", and this table should be updated with new data. At this point, system biology is the well-matched discipline to define constants for interactions, phenotypes, expression *etc*. This is also considered that all variations should be defined to formulate a constant, but it does not seem very likely due to yet unobserved variations and/or unpredictable variations.

Third, it is hard to determine all the associative factors for each supposed fine-tuning. I believe that biology also has laws or rules but not as defined for sciences based on physics and mathematics. This may require the revisiting of meaning or concept of "law" for extensive definitions or for biology only. This need is based on

[17] Dhar and Giuliani, 'Laws of Biology: Why so Few?'
[18] Trevors and Saier, 'Three Laws of Biology'.

the different nature of science, as physics is measurable and predictable, but biology is subject to have natural deviations from certain predictions. Some of these natural deviations have been revealed but there are enormous unknowns in living systems as well.

Although the concept of fine-tuning and laws should be reconsidered in biology, this study suggests "**parameters of excellence**" at molecular level in a human body that can be considered in the concept of fine-tuning. A parameter in biological context is a condition in which its absence or abnormality is associated with abnormal health conditions or death. Therefore, we should say that a parameter is important for adjusting living events, and biological parameters can be considered as fine-tuning of life. These parameters include 1) position, 2) interaction, 3) amount and 4) timing. These parameters are tightly associated with five levels including a) molecule, b) gene, c) genome, d) cell and e) organism levels **(Table 1)**. "Level" means "a place(s)" or "a location(s)" where the molecular event occurs and/or to what extent a parameter affects a living system. These parameters are not independent from each other (discussed later).

Candidate fine-tuning fundamental contexts in molecular biology

A human body is composed of almost 400 types of cells with different functions but work together by well-established communications between each other. The cellular software has been stored within the cell nucleus including two operating systems, i) genome and ii) epigenome. Both genome and epigenome manage gene expressions in harmony during permanent and/or temporary cellular processes. Therefore, we can consider that cells are micro-universes with their own rules. These rules are regulated by four main parameters of excellence: 1) position, 2) interaction, 3) amount and 4) timing.

Position

Epigenetic or mistaken modifications

Genes can be mutated by changing in DNA sequence (called as genetic changes) and/or modified by reversible chemical reactions such as DNA methylation without changing DNA sequence (epigenetic modifications). Mutations are rare events with important roles in evolution, some provide interindividual genomic differences (as single nucleotide polymorphisms), some are with no biological effect, or some are associated with pathological conditions. Epigenetic changes are not mutations due to their reversible characteristics, but they are also inheritable to the next generations. Epigenetic patterns allow a genome to be able to perform differential

gene expression in distinct types of cells of a person. This dynamism indicates a flexible representation of the genome, called epigenome.

From the epigenetic perspective, the modified position of the cytosine base is crucial. If it is modified with a methyl group at the 3rd position, this causes DNA damage which needs to be repaired as soon as possible. However, the modification with a methyl group at the 5th position, called an epigenetic modification, does not cause DNA damage but provides alternative representation of expression of the methylated gene **(Figure 1)**. This suggests that a fine-tuning by position specifies a modification as abnormal (resulting in a damage of a gene) or normal (resulting in epigenetic regulation of a gene). But this is not the sole example but there are many similar events in biological chemistry.

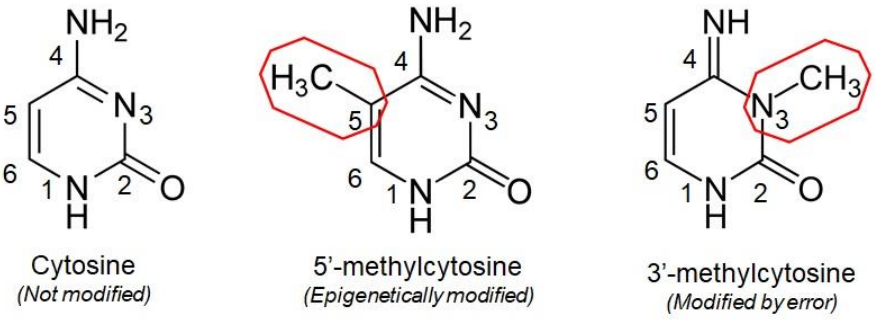

Figure 1. Three forms of cytosine base in the DNA. Ontological structure of cytosine (left), epigenetically modified by a methyl group at the 5th position (middle), incorrect addition of methyl group at the 3rd position (right).

Intragenic modifications

There are four types of epigenetic modifications occurring on DNA with addition of a methyl (-CH_3), a hydroxyl (-OH), a formyl (-COH) and a carboxyl (-COOH) groups to cytosines, respectively. The biological effects of each modification are diverse as DNA methylation is mostly associated with gene inactivation but DNA hydroxymethylation with gene activation [19]. However, this is not that simple. The intragenic position of DNA methylation, for instance, affects gene expressions in diverse ways. A typical human gene has two main parts including regulatory regions (*i.e.*, promoters) and gene body (exons and introns) **(Figure 2)**. The effect of methylation varies depending on its location throughout the gene as it represses gene expression when it occurs on promoter regions while increases the expression

[19] Kitsera et al., 'Functional Impacts of 5-Hydroxymethylcytosine, 5-Formylcytosine, and 5-Carboxycytosine at a Single Hemi-Modified CpG Dinucleotide in a Gene Promoter'.

when it occurs on exon regions [20]. Besides, DNA hydroxymethylation was mostly found on DNA of brain cells [21] suggesting that epigenetic modifications mediate tissue-specific activities.

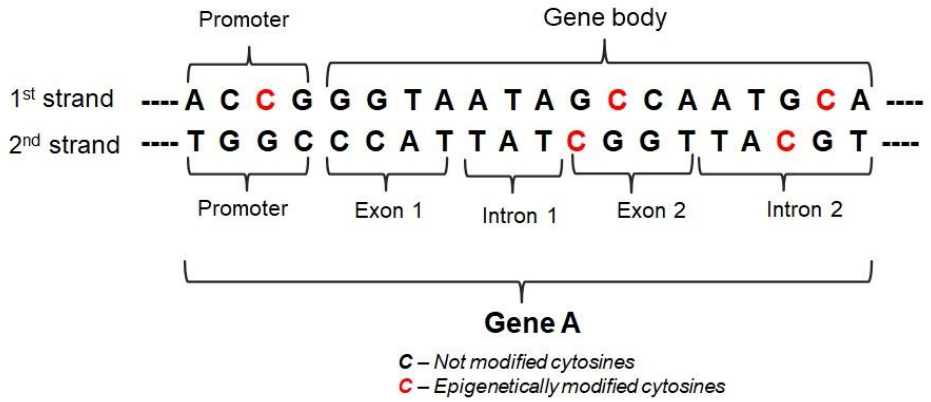

Figure 2. Representative epigenetic modifications (DNA methylation) within a gene

The other aspect of epigenome includes modifications occurring on histone proteins packaging of DNA to form chromatin structure. Epigenetic modifications on DNA and histones regulate gene expressions. These can affect the genome individually, while the crosstalk between these two aspects of epigenetics fine-tunes the gene expression. These modifications provide cell specification to create different types of cells from a cell (zygote). If there was no fine-tuning in gene expression, there would be no different type of cells.

Genomic imprinting

Genomic imprinting is defined as a parent-of-specific monoallelic expression of some genes in the human genome. Diploid genomes have genes with two alleles (maternal and paternal), and most human genes are expressed by both alleles. But some genes (imprinted genes) are specifically expressed in terms of the paternal origin **(Figure 3)**. It means that some genes are maternally expressed, some are paternally expressed. The importance of true establishment of imprinting is revealed by pathological outcomes that occur in case of exchanging the imprint pattern, *e.g.*, when maternally expressed genes in normal conditions are paternally or *vice versa*. For instance, the maternal copy of the *H19* gene is expressed but its

[20] Jjingo et al., 'On the Presence and Role of Human Gene-Body DNA Methylation'.
[21] Khare et al., '5-HmC in the Brain Is Abundant in Synaptic Genes and Shows Differences at the Exon-Intron Boundary'.

paternal copy is silenced by DNA methylation-mediated imprinting. However, the *IGF2* gene is expressed paternally while its maternal copy is imprinted and therefore not expressed. If this pattern occurs in other ways, different syndromes (*i.e.*, Prader-Willi and Angelman syndromes) are formed **(Figure 3)**.

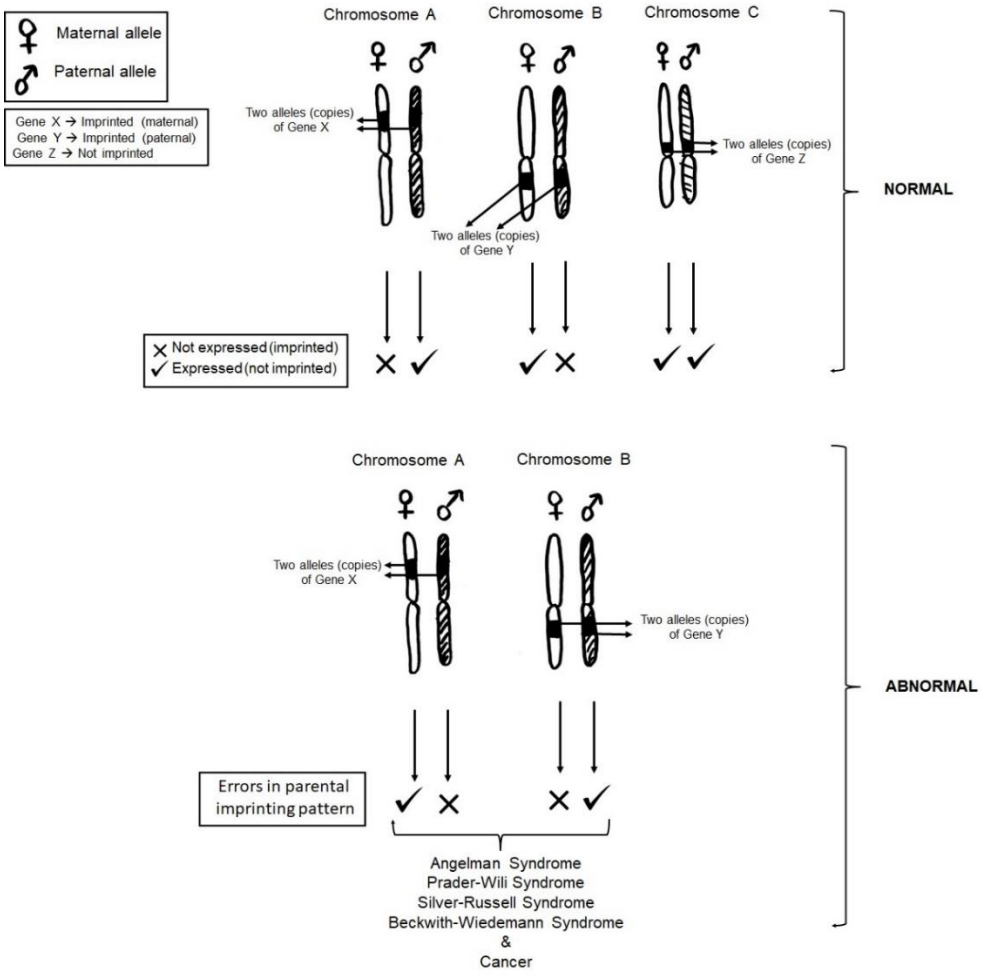

Figure 3. Imprinted (represented by genes X and Y) and non-imprinted genes (represented by gene Z) in normal and abnormal conditions.

Cis and trans elements

Latin terms “cis“ and “trans“ mean “on this side” and “on the other side”, respectively. Cis and trans elements are used to represent genes located on the same

chromosome or on different chromosomes, respectively. For instance, imprinted gene couples are at cis position to each other. These imprinted genes are also at cis position to be managed by cis-located enhancers. Imprinted genes *H19* and *IGHF2* mentioned above are found on the same cytological band, 11p15.5. Additionally, trans-elements are the genes/regions found on different chromosomes than the interacting gene(s). For instance, transcription factors (TFs) are the proteins functioning the regulation of other genes and these factors are encoded by the genes which are in the trans position of genes regulated by. One of the foremost TFs is p53 protein which regulates more than 15 genes and interacts with these genes in response to different conditions (see "Interaction").

Tissue specific expressions

Each human body has its unique DNA code as well as sharing common sequences with ancestries. After fertilisation, zygote forms a new human by dividing as well as undergoing differentiation. Cell division without differentiation fails to create an embryo so that cells should be also differentiating and migrating to relevant parts of the embryo. DNA sequence is rigid and stable in all cells while differentiation, but gene expression profiles change during differentiation to form different cells. The variation between expression levels of gene sets is managed by epigenetic patterns therefore transcription is fine-tuned for creation of different cells, tissues, organs that finally form the organism [22]. Gene expression patterns are also fine-tuned in specific events such in immune response against cancer [23].

Interaction

Transcription factors

Genes are the codes in determining the features of an organism which are translated into RNA and/or protein to function. Proteins are the main biochemical compounds and specifically structured for specific functions. Proteins work in association with each other. This association is not random, but their 3D spatial organisation and chemical properties allow them to establish specific interactions within the cellular pathways. For instance, p53 protein as a TF, functions to manage different cellular pathways involved in apoptosis, cell cycle arrest, prevention of metastasis and angiogenesis [24] **(Figure 4)**. p53 protein is the main regulator to

[22] Wang et al., 'Quantifying the Waddington Landscape and Biological Paths for Development and Differentiation'.
[23] Michaels et al., 'Precise Tuning of Gene Expression Levels in Mammalian Cells'.
[24] Tang et al., 'Mutant P53 on the Path to Metastasis'; Meek, 'The P53 Response to DNA Damage'.

direct cells to a cell fate regarding cellular conditions. The interaction of p53 with which of the proteins depends on the external and internal stimuli received by the cell. If DNA is damaged, the cell first tries to fix it by activating the DNA repair mechanism. In this case, p53 interacts with the DNA repair proteins such as GADD45 and lets cells arrest in the cell cycle for damage fixation [25]. After DNA is repaired, p53 leaves the scene with its decreased level. But if the damage persists, p53 is still active with high levels to change the way for the cell, directing the activation of apoptosis (cell death).

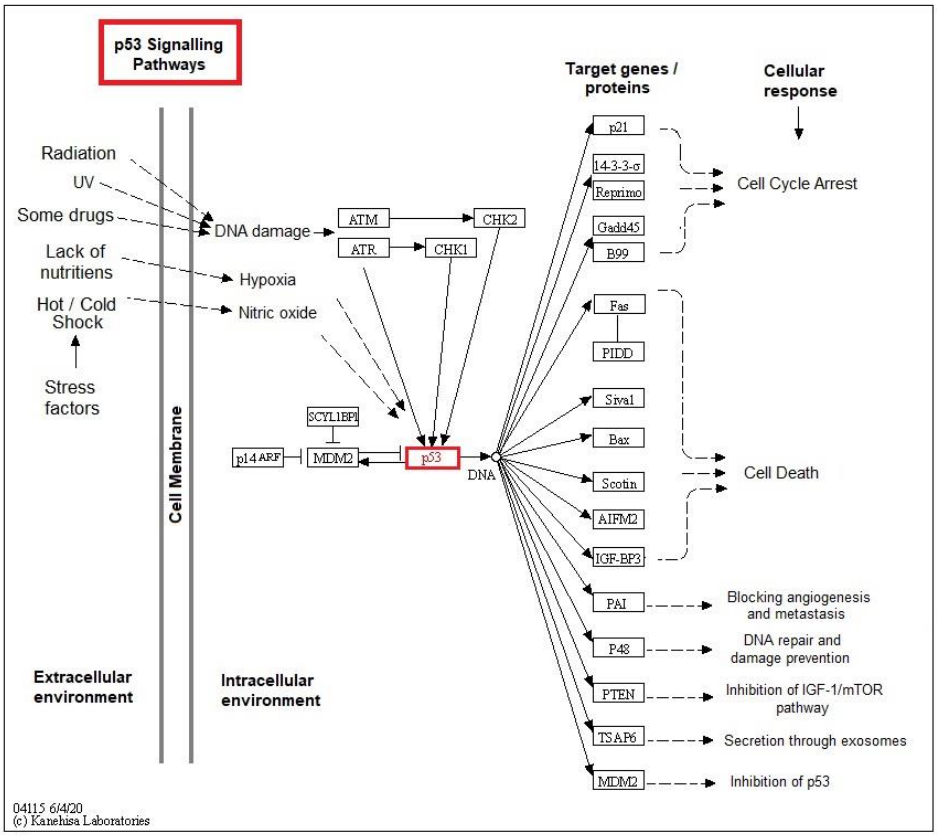

Figure 4. Representative diverse cellular pathways managed by interactions of a protein, p53, with different proteins *(revised from KEGG pathway database)*.

Enzymes and substrates

Enzymes are the biggest protein family catalysing specific biochemical reactions to activate/inactivate cellular events. Each enzyme has its own substrate The

[25] Han et al., 'GADD45a Mediated Cell Cycle Inhibition Is Regulated by P53 in Bladder Cancer'.

dockings of enzymes to substrates are not random. Substrates can be either protein or non-protein compounds such as carbohydrate, DNA and RNA *etc*. Caspases are the specific protease sub-family with 7 enzymes [26] that function in cell death by hydrolysing proteins into smaller peptides. A study reported that Caspases 2, 3, 6, 7 and 8 have the affinities for slightly different substrates while structure of caspases are similar to each other to some extent [27]. Another enzyme group, phosphatases which are responsible for protein (de)activation, have specific domains in their substrates to recognize [28]. These suggest specific interaction between each protease with substrates. All the enzymes not mentioned here function in a similar manner. Otherwise, non-specific interactions between enzymes and substrates would lead to chaos in the cells thereby collapsing cellular activities very soon.

Ligands and receptors

Receptor proteins also function by the interaction of specific ligands (another protein family). Receptor proteins are embedded into cell membranes and responsible for transmission of extracellular signals towards the inside of the cells. This transmission is managed by the activation of receptors with their ligands. After an extracellular signal is received, an intracellular response is initiated. Response starts as soon as the activation of receptor with ligands (step 1), the example mechanism includes then the intracellular domains of receptors are phosphorylated by forming homodimers of receptor (step 2), activation of homodimeric receptors activate a relevant protein involved in specific cellular responses (step 3), and the signal is transferred into cell nucleus by sequential activation of other involved proteins (step 4). The general term to define this mechanism is "cell signalling". There are a range of cell signalling pathways to direct cells to different actions **(Figure 5)**.

[26] Boice and Bouchier-Hayes, 'Targeting Apoptotic Caspases in Cancer'.
[27] Zhou et al., 'Deep Profiling of Protease Substrate Specificity Enabled by Dual Random and Scanned Human Proteome Substrate Phage Libraries'.
[28] Li et al., 'Elucidating Human Phosphatase-Substrate Networks'.

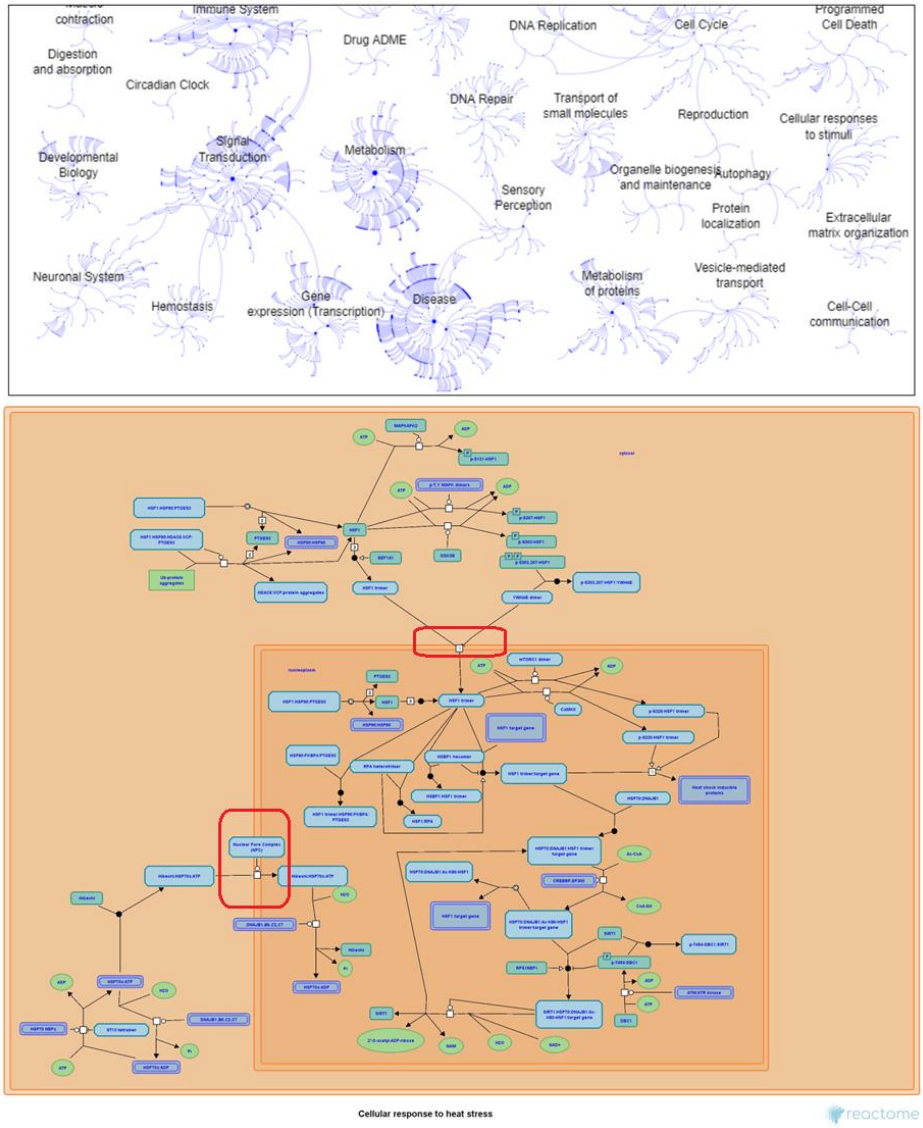

Figure 5. Cellular pathway networks by Reactome database[29]. The upper panel shows classification of cellular events (each blue line indicates a specific pathway), the lower panel shows representative cellular pathways involved in cell response to heat stress. Red squares show the interactions of ligands with receptors specifically functioning in this response. These pathways also support "interaction" parameter.

[29] Fabregat et al., 'Reactome Diagram Viewer: Data Structures and Strategies to Boost Performance.'

Amount

Low and high levels of proteins

Tissue-specific genes are the genes that encode proteins only in specific cells. For instance, insulin hormone is produced in a specific subtype of pancreas cells, beta cells only (also associated with "position" parameter). However, all cells of humans have a genetic code for insulin secretion. This is the way hormones work. Hormones are produced in specific cells with prominent levels, but their overall level in the body is low. This fine-tuned level is reasonable for biological function.

Other proteins are not tissue-specific and called "housekeeping-genes". These are expressed at relatively low levels in all cells, but this level is enough for maintenance of vital functions in the cells. For instance, p53 is a housekeeping protein required for all cells. However, it exists at low level and in inactive form by being blocked with another protein, MDM2, a negative regulator of p53 (interaction) [30]. When p53 protein is needed as mentioned above, its level increases soon after its activation by unbounding from MDM2 (associated with "interaction" parameter). Similarly, the level of some immune-related proteins defines the immune response when needed [31]. Therefore, these suggest that protein levels are adjusted in the cells according to 1) requirement of the protein at that condition and/or 2) permanent or temporary requirement of the protein at a certain time.

The interaction between levels of different types of molecules

The best model for this is that mRNA and protein levels are associated with each other. mRNAs are the molecules translated into proteins. Not surprisingly, protein levels in the cells vary depending on the corresponding levels of mRNA for a specific gene, but it is noteworthy that this interaction between the levels alters according to cell type and the cellular conditions [32]. This suggests that interaction, level, and position are correlated.

Timing

Circadian rhythm

All the parameters are associated with each other and regulated by time. The most notable event in the human body about time is the circadian rhythm (also

[30] Brooks and Gu, 'P53 Ubiquitination: Mdm2 and Beyond'.
[31] Michaels et al., 'Precise Tuning of Gene Expression Levels in Mammalian Cells'.
[32] Liu, Beyer, and Aebersold, 'On the Dependency of Cellular Protein Levels on MRNA Abundance'.

called as the biological clock). This is a systemic event working in harmony with the solar system. This is managed by the secretion level of hormones and the activation of different genes regarding the intensity of daylight. For example, melatonin is a hormone also known as a "sleep hormone" that starts being released at 9 p.m. and stops being released around 7 a.m. On the other hand, the genes regulating the circadian rhythm can basically be divided into two groups as "daytime" and "nighttime" genes. *BMAL* and *CLOCK* genes are the leading genes actively working in daylight. Conversely, *PER* and *CRY* genes work actively at night during sleep[33]. Two groups of genes are negative regulators to each other.

The regulation of the human body by such a rhythm is fine-tuned by the balance between activation and deactivation of genes and hormones adjusted to such a circle. If this system is impaired somehow (for instance regularly being awake during night-time), susceptibility to some diseases such as cancer [34], sleep disorders and circadian rhythm diseases [35] increases.

Crossing over

A human genome consists of the genomic information of both parents. Each parental germ cell (sperm and oocyte) has its own genetic pattern (from ancestries), and these patterns are rearranged by crossing-over before fertilisation. Crossing-over only occurs in meiosis to recombine genetic information before transmitting it to next generations. This provides genetic variability between individuals even if they are born from the same parents. Meiosis takes place in only germ cells (location) at a certain time during spermatogenesis or oogenesis.

Hormones

Hormones are the molecules mostly in protein structure and produced by genes. The mechanisms of action of hormones highly depend on tissue/cell specificity, time, and level. For instance, different sets of hormones are secreted during the menstrual cycle in females. The balance between menstrual hormones dynamically changes during the cycle to maintain the normal mechanism of reproduction. The abnormalities in the hormonal system can lead to fertility problems.

[33] Trott and Menet, 'Regulation of Circadian Clock Transcriptional Output by CLOCK:BMAL1'.
[34] Han et al., 'Circadian Rhythm and Melatonin in Liver Carcinogenesis: Updates on Current Findings'.
[35] Rijo-Ferreira and Takahashi, 'Genomics of Circadian Rhythms in Health and Disease'.

Neurotransmitters

Neurotransmitters function in the synaptic communication between the neurons therefore they are released to an extracellular region, called synaptic gap, from a neuron. The neurotransmitter molecule is then taken by the interacted neuron. But this transfer should be very fast. The prolonged existence of neurotransmitters within the synaptic gap was found to be associated with abnormal neurological functions [36]. This is also important that transport problems are not the only parameter involved in neurological abnormalities but also synthesis and degradation of neurotransmitters after use are.

Conclusions

This study attempts to evaluate fine-tuning in molecular systems of the human body, and suggests four fine-tuned fundamental contexts including position, interaction, amount, and timing by different levels (molecule, gene, genome, cell, and organism) **(Table 1)**. Epigenetic machinery is one of the best representatives for molecular fine-tuning in the regulations of gene expression [37]. The activation or silencing of a gene is regulated by epigenetic changes at certain times.

Discussions on the fine-tuning argument for molecular biology are highly limited in the literature. To the best of knowledge, there is no study defining parameters in molecular biology that can be considered for the fine-tuning argument. Thorvaldsen *et al.* claimed the use of statistical methods to evaluate fine-tuning in molecular biology, and they argued that living systems have fine-tuning at various levels including 3D spatial structure of proteins, protein complexes and cell signaling pathways. The design is based on "irreducible complexity" and "specified complexity" suggesting that FTA in molecular biology can be formulated by statistical models not by "the eyes of the beholder" [38]. Changes in one or two parameters that manage the universe can often balance the other that is changed [39]. This is, of course, not interesting, because parameters are not independent from each other. The mathematical formulas are the equalities in balance, and statistical models are to conclude if there is randomness or the specificity.

The fine-tuning conclusion of molecular events in the cells is not incompatible with Darwinian evolution. Darwinian evolution theorizes the natural selection of species and suggests that not only dominant genetic features are

[36] Siu, 'Genetics of Monoamine Neurotransmitter Disorders.'
[37] Mohtat and Susztak, 'Fine Tuning Gene Expression: The Epigenome'.
[38] Thorvaldsen and Hössjer, 'Using Statistical Methods to Model the Fine-Tuning of Molecular Machines and Systems'.
[39] Barnes, 'The Fine-Tuning of the Universe for Intelligent Life'.

maintained but also abnormal cells/organs are degraded. Abnormality in the cells is derived from the disruption in the fine-tuned system based on the central dogma and other intra/extracellular activities, and abnormal cells are subject to be eliminated to maintain the homeostasis of the human body. Thus, biological evolution allows cells/organisms to generate and inherit in an appropriate way, and the maintenance of fine tuning of living matter may utilize evolution by natural selection.

I think that FTA defined by molecular biology may be an alternative explanation for the question why we observe our universe to be fine-tuned as asked by proponents of Multiple Universes (MU). Because multiple universes explain why some universe is fine-tuned. MU thus seems to provide a plausible naturalistic alternative to design explanations of fine-tuning, consistent with the anthropic principle [40]. Our universe has been fine-tuned in terms of physical settings which may then induce the fine tuning of living defined by molecular biology.

Human (biological species name as *Homo sapiens*) is the most sophisticated species in terms of biological and cognitive functions. Therefore, this study focuses on humans only. But other eukaryotic living things including plants and animals have similar molecular pathways and mechanisms. The differences between the human body and other organisms are the chemical structure of proteins (amino acid sequences and 3D architecture) and the sequence of genes. However, many proteins have conserved domains between species, and different species have orthologous genes. The slight changes in structures result in different species and these biomolecular molecules perform similar activities in the cells. Primitive forms of these mechanisms also occur in prokaryotes such as bacteria. It suggests that the fine-tuning argument can be also applicable for other species, and this phenomenon is also compatible with Darwinian evolution.

This study deals with the definition of laws and randomness along with the existence of fine-tuning in molecular biology. As a conclusion, it suggests a new fine-tuning class regarding to molecular biology in addition to four fine-tuning classes discussed by Robin Collins including 1) fine-tuning of physics laws, 2) fine-tuning of physics constants, 3) fine-tuning of the beginning of life, and 4) fine-tuning in forming chemical elements [41]. FTA should be considerable for other species including plants in addition to humans. All living species have similar molecular systems. Thorvaldsen *et al.* concluded fine-tuning clearly exists in biological systems even more complex than in inorganic systems. Therefore, FTA in molecular biology needs to be studied more comprehensively in association with different disciplines

[40] Manson, 'The Fine-Tuning Argument'.
[41] Collins, 'God, Design, and Fine-Tuning'.

including mathematics, statistics, bioinformatics, philosophy, molecular biology, genetics, and biological chemistry.

Table 1. Fine-tuning parameters in molecular events at different levels

Fine-Tuning Parameter	Molecular event	Examples	Level
Position	Epigenetic or mistaken modifications on bases	Epigenetic modification; 5meC or DNA damages by; 3meC, adenine methylation	Molecule level
	Intragenic modifications	Different effects of DNA methylation occuring on promoters or on gene bodies	Gene level
	Genomic imprinting	Parent-of-origin specific imprinted genes (*H19* and *IGF2* genes)	Gene and Genome levels
	Cis and trans elements	Enhancer regions for gene regulation	Genome level
	Tissue specific expressions	Insulin and other hormones	Cell level
Interaction	Gene regulation	Transcription factors (such p53)	Molecule and gene levels
	Biochemical reactions	Enzymes	Molecule level
	Ligand-receptor interaction	Hormones and their receptors in the cell membrane	Cell level
Amount	Low levels	p53, hormones	Cell and organism levels
	High levels	Housekeeping proteins	Cell and organism levels
Timing	Circadian rhythm	Secretion of hormones regarding day light	Gene and organism levels
	Crossing-over	Genetic rearrangement during meiosis in germline	Cell level
	Endocrine system	Hormones in some certain times (such as during menstrual cycles)	Organism level
	Nervous system	Neurotransmitters	Organism level

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