

On the Neglected Shifting balance theory, Bateson–Dobzhansky–Muller model & Quantum evolution plus the Role of Mitochondrial Membrane Potential (MMP) Impact on COVID-19

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Abstract

Background: Approximately 80% of all viruses are RNA viruses and they contain their specific RNA helicases. Defective RNA helicases have been linked to infectious diseases (Viral Infections).

Materials and Methods: The articles have gone through many types of research from the beginning of the epidemic of Coronaviruses through history and we introduced the neglected hypothesis of Shifting balance theory, Bateson–Dobzhansky–Muller model & Quantum evolution. In the ancestral population, the genotype is AABB. When two populations become isolated from each other, new mutations can arise. In one population A evolves into a, and in the other B evolves into b. When the two populations hybridize it is the first time A and B interact with each other. When these alleles are incompatible, we speak of Dobzhansky–Muller incompatibilities plus the role of MMA in mitochondria in spreading SARS-CoV-19 through populations and the result of an infection in COVID-19.

Results: In viruses specifically COVID-19, Ribosomal Frameshift is programmed to allow the virus to encode multiple types of proteins from the same mRNA. HIV-1 (human immunodeficiency virus), RSV (Rous sarcoma virus), and all types of influenza viruses use Ribosomal Frameshift. They rely on frameshifting to create a proper ratio of normal translation and trans-frame (encoded by frameshifted sequence) proteins. Notably, its use in viruses is primarily for compacting more genetic information into a shorter amount of genetic material.

Conclusion: to find the genome sequence of COVID-19 we also used Nanopore sequencing that introduced and manufactured by Oxford scientists, due to differences in the action of infection in the host, we could not reach any results since the Novel Virus has not a stable genome (which is quite dynamic) since through our deep research, each virus contains its specific genome sequencing and we cannot claim that COVID-19 has one specific genome sequence like MERS-CoV, SARS-CoV or any types of viruses which has been discovered and contains their specific genome.

Keywords: Shifting balance theory, COVID-19, MMP, Bateson–Dobzhansky–Muller model & Quantum evolution

Introduction

Coronaviruses were discovered in the late 1930s [1]. Arthur Schalk and M.C. Hawn found out in 1931 a novel respiratory infectious disease which called nowadays Coronavirus Disease, in North Dakota. The infected chickens' mortality rate was 40 percent to 90 percent which was really important [2]. Fred Beaudette and Charles Hudson isolated and cultivated the infectious bronchitis virus which caused Coronavirus Disease [3]. In 1940, during the second world war, two more animal coronaviruses, mouse hepatitis virus (MHV), and transmissible gastroenteritis virus (TGEV) were detected and isolated [4]. It was not recognized by the scientists that at that time that these three different viruses were related to Coronavirus [7]. Human coronaviruses were discovered in the 1960s [5-

6]. They were cultivated and isolated using two different patterns in the UK and the United States of America. [8] E.C. Kendall, Malcom Byone, and David Tyrrell in 1960 isolated from a male human a new common cold virus which called B814 [9-11]. The virus, unfortunately, could not be able to be cultivated using first standard techniques which had successfully cultivated rhinoviruses, adenoviruses, and other known common cold viruses. In 1965, Tyrrell and Byone [12]. The new cultivating method was discovered and introduced to the laboratory by Bertil Hoorn [13]. The isolated virus when intranasally inoculated into volunteers caused a cold and was inactivated by ether which indicated it had a lipid envelope [14-15]. At the same time, Dorothy Hamre [16] and John Procknow from the University of Chicago isolated 229E virus from medical students, that they grew in their kidney tissue culture. The

novel/new virus 229E, like the virus B814, when inoculated into volunteers caused a cold and was inactivated by ether. [17] B814 and 229E viruses were imaged by electron microscopes in 1967 by Scottish virologist June Almeida at St. Thomas Hospital in London. [18-19] Not only B814 and 229E viruses were related to each other, but also they were morphologically being in relation to infectious bronchitis virus (IBV). [20] A research group at the NIH at the same year were able to isolate another member of this novel group of viruses by using organ culture and named the virus strain OC43. [21] Like B814, 229E, and IBV, the new cold virus OC43 had distinctive when observed with the electron microscope. [22-23] The IBV-like novel cold viruses were shown to be morphologically related to the mouse hepatitis virus. [24] This new group of IBV-like viruses discovered as coronaviruses after their distinctive morphological appearance. [25] Human coronavirus 229E and OC43 continued to be studied for years. [26-27] The coronavirus strain B814 was lost. It is not known which present human coronavirus it was. [28] Other human coronaviruses discovered and named SARS-CoV in 2003, HCoV NL63 in 2004, HCoV HKU1 in 2005, MERS-CoV in 2012, and SARS-CoV-2 in 2019 which we call it COVID-19. [29-30] There have also been a large number of animal coronaviruses identified since the 1960s which shows these strains of viruses are high in number and very difficult to be studied one by one. [31]

Origin

The recent common ancestor (MRCA) of all coronaviruses is estimated to have existed in 8000 BCE, although some models place the common ancestor in 55 million years or more, implying long term co-evolution with bat and avian species. [32] The most recent common ancestor of the alpha-coronavirus has been placed in 2400 BCE, of the beta-coronavirus line at 3300 BCE, of the gamma-coronavirus line at 2800 BCE, and of the delta-coronavirus line at about 3000 BCE. Bats and birds, as warm-blooded flying vertebrates, are an ideal natural reservoir for the coronavirus gene pool. Bats are the reservoir for alpha-coronaviruses and beta-coronavirus. However; birds are the reservoir for gamma-coronaviruses and delta-coronaviruses. The large number and global range of bat and avian species that host viruses have enabled extensive evolution and dissemination of coronaviruses from the first till today which means these species are the best hosts for evolution of Coronaviruses. [33]

Most human Coronaviruses have their origin in bats. [34] The human Coronavirus strain NL63 has a common ancestor with a bat coronavirus (ARCoV.2) between 1190 and 1449 CE. [35] The human coronavirus strain 229E shared a common ancestor with a bat coronavirus (GhanaGrp1 Bt CoV) between 1686 and 1800 CE. [36] Recently, alpaca-coronavirus and human coronavirus strain 229E diverged sometime before 1960. [68] MERS-CoV emerged in humans from bats through the intermediate host of camels. [37] MERS-CoV, related to several bat coronavirus species, appears to have diverged from these several centuries ago. [38] The most closely related bat coronavirus and SARS-CoV diverged in 1986. [39] A possible line of evolution of SARS coronavirus and keen-bat-coronaviruses is that SARS related coronaviruses evolved in bats for a long period of time. The ancestors of SARS-CoV first infected leaf-nose bats of the genus *Hipposideridae*; they spread to horseshoe bats in the species *Rhinolophidae*, then to civets, and finally to humans. [40-41]

All discussions above can be reduced in words to: (SARS-CoV to *Hipposideridae* to *Rhinolophidae* to *Civets* to Humans).

Unlike other Beta-coronaviruses, bovine-coronavirus of the species Beta-coronavirus 1 and subgenus Embecovirus is thought to have originated in rodents and not in bats. [42-43] In the 1790s, equine coronavirus diverged from the bovine coronavirus after a cross-species jump. [44] Later in the 1890s, human coronavirus OC43 diverged from bovine coronavirus after another cross-species spillover event. [45-46] It is speculated that the flu pandemic of 1890 may have been caused by this spillover event, and not by the influenza virus, because of the related timing, neurological symptoms, and unknown causative agent of the pandemic. [47] Besides causing respiratory infections, human coronavirus OC43 is also suspected of playing a role in neurological diseases. [48] In the 1950s, the human coronavirus strain OC43 began to turned into the present genotypes. [49] Phylogenetically, mouse hepatitis virus which is called Murine coronavirus, that infects the mouse's liver and central nervous system, [50] is related to human coronavirus OC43 and bovine-coronavirus. Human coronavirus HKU1, like the aforementioned viruses, also has its origins in rodents. [51] Well-known rodents include mice, rats, squirrels, prairie dogs, chipmunks, chinchillas, porcupines, beavers, guinea pigs, hamsters, gerbils, and capybaras. Rabbits, hares, and pikas.

Materials and Methods

As described in above lines, SARS-CoV-2 is a complex virus. the genome of the virus differs from one person to another like fingerprints in humans and the reason behind this phenomenon is the amount of tRNA and the metabolism or better called Mitochondrial Function of the person which is based on the amount of ATP releasing from the Mitochondria of each cell and loss of MMP (mitochondrial membrane permeabilization) which is the reason behind the cause of cell apoptosis. Mitochondrial ATP needs proteins from the nuclear and mitochondrial genomes. ROS (Reactive Oxygen Species) disrupt the oxidative production of ATP, which is needed for normal cellular function, Because of the damage of mtDNA that disrupts the normal synthesis of proteins which is needed for mitochondria function, making them suitable targets for attacks by ROS produced during infections by viruses including Coronaviruses that raises ROS in the host cell which affects Mitochondria and leads to loss of MMP. [52]

Proteins are translated by reading tri-nucleotides on the mRNA strand, also known as codons, from one end of the mRNA to the other (from the 5' to the 3' end). Each codon is translated into a single amino acid. Therefore, a shift of any number of nucleotides that is not divisible by 3 in the reading frame will result in subsequent codons to be read differently. [53] This effectively changes the ribosomal reading frame. In viruses specially COVID-19, Ribosomal Frameshift is programmed to allow the virus to encode multiple types of proteins from the same mRNA. HIV-1 (human immunodeficiency virus), [54] RSV (Rous sarcoma virus) [55], and all types of influenza viruses use Ribosomal Frameshift. they rely on frameshifting to create a proper ratio of normal translation and trans-frame encoded by frameshifted sequence proteins. Importantly, its use in viruses is primarily for compacting more genetic information into a shorter amount of genetic material.

Effect of RNA Helicase in COVID-19

Helicases are enzymes that are important to all living organisms. Their main action is to unpack an organism's genes. They are motor proteins that move directionally along a nucleic acid phosphodiester backbone, separating two annealed nucleic acid strands such as DNA and RNA using energy from ATP hydrolysis which proves that the vital COVID-19 is dependent on the amount of ATP production of the host cell by mitochondria. Approximately 1% of eukaryotic genes codes for helicases.

[56] The human genome codes for 95 non-redundant helicases: 64 RNA helicases which is important in infection of SARS-CoV-2, and 31 DNA helicases. Many cellular processes, such as DNA replication,

transcription, translation, recombination, DNA repair, and ribosome biogenesis involve the separation of nucleic acid strands that necessitates the use of helicases.



Figure (1): the different promoter sequences and accessory domains that aid in RNA unwinding. The red regions are ATP binding domains and the yellow regions are RNA interaction domains. Specific sequences termed DEAD-box proteins are also present that help catalyzes reactions in which ATP does not need to be directly hydrolyzed, as long as it binds to the domains on the strand.

This image represents the different promoter sequences and accessory domains that aid in RNA local strand separation. The red regions are ATP binding domains and the yellow regions that is RNA interaction domains.

Special sequences termed DEAD-box proteins helps catalyzes reactions in which ATP does not need to be directly hydrolyzed, as long as it binds to the domains on the strand.

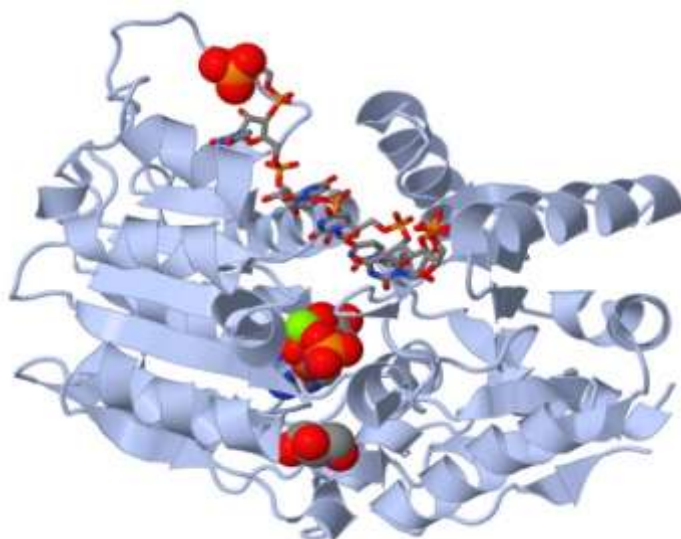


Figure2. Human DEAD-box RNA helicase

Nearly 80 percent of all viruses are RNA viruses and they contain their specific RNA helicases. [58] Defective RNA helicases have been linked to Viral Infections. [59] Some RNA helicases and DNA helicases can be found together in all the helicase super-families except for SF6. [60] [61] All the eukaryotic RNA helicases that have been identified till present days are non-ring forming and are part of SF1 and SF2. Ring-forming RNA helicases have been found in bacteria and viruses. [62] RNA helicases that do exhibit unwinding activity have been characterized by at least two different mechanisms: 1. canonical duplex unwinding and 2.

local strand separation. local strand separation happens by a process wherein the helicase enzyme is loaded at any place along with the duplex. This is usually aided by a single-strand region of the RNA, and the loading of the enzyme is accompanied by ATP binding. [60] Once the helicase and ATP are bound, local strand separation happens, which needs the binding of ATP, but not the actual process of ATP hydrolysis. [62] Presented with fewer base pairs, the duplex then dissociates without further assistance from the enzyme. This mode of unwinding is used by the DEAD/DEAH box helicases. [63]

| | |
|---------------------|--------------|
| RNA helicase | |
| Identifiers | |
| EC number | 3.6.4.13 |
| Databases | |
| IntEnz | IntEnz view |
| BRENDA | BRENDA entry |

| | |
|-----------------------|----------------------|
| ExPASy | NiceZyme view |
| KEGG | KEGG entry |
| MetaCyc | metabolic pathway |
| PRIAM | profile |
| PDB/structures | RCSB PDB PDBe/PDBsum |

Table 1. The table shows RNA Helicases [64] [65] [66]

In Vitro, to find the specific helicase activity of COVID-19, we used fluorescence-based assays, filtration assays, a scintillation proximity assay, a time-resolved fluorescence resonance energy transfer assay, and even used Trupoint diagnostic assay to observe the Helicase Activity. Even we have used the basic strand displacement assay which had been used in 1982–1983. [67] [68] The result was interestingly showed each Virus Helicase Assay is different from the other. The reason is the environment where the virus exists/evolves rapidly and the only answer to this result is Lamarckian Evolution. As Coronaviruses Including SarS-CoV-2 evolves very fast, their adaptation to the environment explains our results. [67] [68] [69]

Shifting balance theory, Bateson–Dobzhansky–Muller model & Quantum evolution

The Bateson–Dobzhansky–Muller model, [69] is a model of the evolution of genetic incompatibility, important in comprehending the evolution of reproductive isolation during speciation and the role of natural selection (Darwin Theory) in bringing it about. The theory was first presented by William Bateson in 1909, [70] after that by Theodosius Dobzhansky in 1934, and then by Herman Muller, H. Allen Orr, and Sergey Gavrilets. [71]. This model describes the drift between two species or even viruses to become hybrid and act differently in the environment. As many scientists only focus on the Co-Evolution of the viruses, Bateson–Dobzhansky–Muller model can be useful in describing the Fixation and Adaptation of SARS-CoV-2 and COVID-19 in the different environment as well.

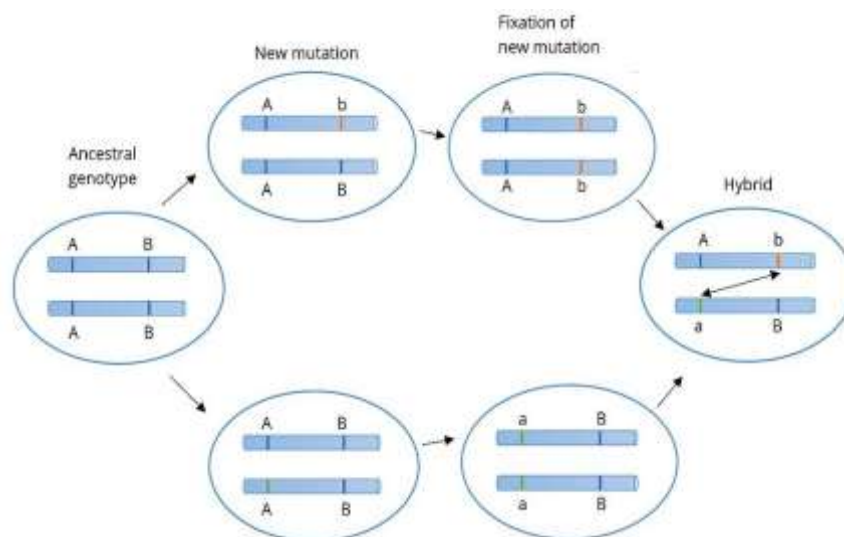


Figure3. Bateson–Dobzhansky–Muller

In the ancestral population, the genotype is AABB. When two populations become isolated from each other, new mutations can arise. In one population A evolves into a, and in the other B evolves into b. When the two populations hybridize it is the first time A and B interacts with each other. When these alleles are incompatible, we speak of Dobzhansky–Muller incompatibilities.

The Shifting balance theory is another theory of evolution introduced in 1932 by Sewall Wright, suggesting that adaptive evolution may proceed most quickly when a population of viruses divides into subpopulations with restricted gene flow. attempting to explain how a population may move across an adaptive valley to a higher adaptive peak. [72] According to the theory, this movement occurs in three steps:

- (1) Genetic drift: allows a locally adapted subpopulation to move across an adaptive valley to the base of a higher adaptive peak.
- (2) Natural selection: will move the subpopulation up to the higher peak.
- (3) This new superiorly adapted subpopulation may then expand its range and outcompete or interbreed with other subpopulations, causing the spread of new adaptations and movement of the global population toward the new fitness peak.

All three steps describe adaption, Genetic Drift, and the Fitness of SARS-CoV-2. Novel Coronavirus has been evolved so fast from their ancestors to become a new Hybrid Novel RNA Virus and like cancer cells, they have rapid genetic mutations and adaptation to the environment.

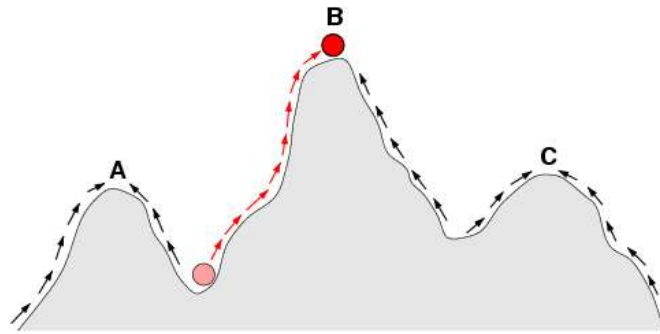


Figure 4. [The arrows indicate the preferred flow of a population (Viruses as well) on the landscape. The red ball indicates a population (or Viruses) that moves from an adaptive valley to the top of an adaptive peak. Based on natural selection (which usually acts to increase fitness in a population), it is not possible for a population at peak A to reach peak B because this requires descending into an adaptive valley. Shifting balance theory aims to explain how this may be possible.

Quantum evolution was introduced by George Gaylord Simpson in 1953. Quantum Evolution happens at the Taxonomic level and it plays a very important role in the origin taxonomic units of relatively high rank in families, orders, and classes of species and parasites including viruses. As a whole, according to Simpson's statements in 1944, quantum evolution resulted from Sewall Wright's model of random genetic drift. [74-83]

The History behind the Neglected Coronavirus

We cannot forget the history of the outbreak of Coronaviruses. Firstly, it was considered harmless pathogens until they caused three major pandemic of severe respiratory disease in the last 20 years. The Coronavirus was recognized in 1960 [84] and it was identified as a cause of the common cold. In 2002, it was considered not fatal virus and not severely pathogenic to humans which was a mistake. Then took place across the globe when an infected doctor traveled to Hong Kong in February 2003 [85] and transmitted the infection to other health workers and guests staying in the same hotel. These patients brought infection back to their home countries, that is, Singapore, Vietnam, and Canada. In the year 2012 [86], a new coronavirus became pandemic in the Middle East and was named Middle East Respiratory Syndrome (MERS). [86--90] Based on our sessions above, the COVID-19 is a Hybrid Virus with has a high mutation rate like cancer cells and has the potential of causing a new Hybrid Pandemic in the future. The Shifting Theory, Co-Evolution, Bateson–Dobzhansky–Muller model, and Quantum Evolution are the reason behind these high rare and neglected pandemics in the last 20 years.

Conclusion

Based on our research, to find the genome sequence of COVID-19 we also used Nanopore sequencing that introduced and manufactured by Oxford scientists, due to differences in the action of infection in the host, we could not reach any results since the Novel Virus has not a stable genome which shows it is quite dynamic. since through our deep research, each virus contains its specific genome sequencing and we cannot claim that COVID-19 has one specific genome sequence like MERS-CoV, SARS-C-V or any types of viruses which has been discovered and contains their specific genome. The main reason is the quick adaptation to the environment, Temperature, humidity, host genome type, host metabolism, Genetic Drift, Recombination of the virus, the high population of human beings, and the amount of ATP production of the host by their Mitochondria and loss of MMP. Therefore; any type of vaccine cannot prevent the host from becoming infected by the virus since as we discussed, the virus is flu based. Vice versa, the new Coronavirus

becomes more adapted and changes rapidly to make the environment and the host becoming weak and infected in the end.

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