the diagnostic pathology journal DIAGNOSTIC PATHOLOGY

Klaus Kayser; diagnostic pathology 2020, 6:280
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2020-6:280

Research

From COVID-19 Infection to social level disease (SLD)

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Abstract

AIM: To analyse, diagnose, and forecast the development of the pandemic Corona disease and to transfer the data into a corresponding virtual 'orders of structure system'.

Background: COVID-19 pandemic is a RNA virus transmitted human respiratory tract infection of moderate to high infection rate (20 % – 40 %) and a case fatality ratio of 2 % – 5 %. The infection rate depends upon age and health condition of exposed persons, density of virus droplets, air temperature, legal regulations as well as social life style and behaviour.

Stage of prevention: The high modulation rate of virus RNA and its protein structure require protective strategies at cellular and macromolecule level (preventive immunization), individual protection (personal risk) such as mouth masks, strict regulations of the social behaviour, shutdown of restaurants, hotels, of travel, public demonstrations, private festivals, etc. Legal regulations often hinder the state and federal government from acting in fully restrictive manner. Numerous citizens are not convinced of the ordered restrictions. They fear severe damage to their 'freedom' and economic situation. Therefore, COVID-19 also causes a social level disease (SLD), and should be diagnosed and treated accordingly.

Explanation and diagnosis of a social level disease (SLD): Nature has organized human life in ordered communicative structures which can be represented by horizontal and vertical coordinates. Horizontally arranged neighbouring structures can often replace damaged or lost structures, in contrast to vertical structures. External interaction, forecast and potential repair of involved structures require statistical algorithms. Calculation of entropy at different structure levels is a useful tool to forecast the disease's course.

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Conclusions and advices: COVID-19 disease is primarily a RNA virus infection which starts at low level structures (macromolecule) and induces alteration of communicative higher order structures. They include primarily pulmonary cells, airways, additional organs, individual persons, human behaviour, profession, trade, organization of societies, states and countries. Severe changes of social behaviour and civil laws are unavoidable consequences. They belong to basic natural laws of communication, droplet distribution, decay of infectious agents and individual protection.

Keywords: COVID-19 pandemic, social level disease, orders of structures, entropy.

Introduction

Virus infections are not uncommon in human being. For example, a heavy outbreak of an influenza pandemics (subtype A/H1N1) infected about 500 Million people during 1918 till 1920 and led to at least 20 Million to 50 Million, or even 100 Million fatal cases. At that time the construction of biological matter and its role in associated functions were only superficially known when compared to the present stage (1-6).

Additional hazardous outbreaks of influenza appeared in China 1957 (subtype A/H3N2, one to two million fatal cases), in Hong Kong in 1968 (subtype A/H3N2, one million fatal cases) and in north China 1977 (subtype A/H1N1, Spanish flu, named Russian flu). For a long time influenza virus infections were considered to be more dangerous than Corona virus infections. This opinion changed dramatically during the first SARS-CoV-1 pandemics in 2002/2003 (1, 8), spreading from Guangdong, South China.

The actual pandemic pulmonary infectious disease COVID-19 (Virus SARS-CoV-2) started in Wuhang, Republic of China. The WHO China Country Office was informed of severe pneumonia of unknown aetiology December, 31, 2019. The first report of an infected patient in Thailand, a generalized spread in China and worldwide infections were noted since March 2020 and later (4, 9-11). The World Health Organization declared the Corona Virus COVID-19 spread as pandemic on March 11, 2020 (9, 12, 13).

Reports of infected persons and disease related deaths followed soon, for example in the USA on January 23, 2020, in Italy, Europe on February 23, 2020.

Symptoms and clinical course of the COVID-19 infection appear as severe (acute) respiratory distress syndrome (SRDS, ARDS).

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Severe acute respiratory syndrome (SARS) gave the (wrong) impression that man-to-man infection might not occur or only rarely. However, detailed investigations soon proved that infected family members without symptoms often infect their partners and children heavily (3, 14-16).

The fast spread and high transmission risk as well as the absence of an effective immunization induced a lockdown of nearly all parts of social life. Hence, a financial, industrial and commercial crisis followed immediately (17-22).

The prevention of a general collapse of the health care system and specifically the insufficient number of essencentially intensive care personal and units forced a disruption of all parts of social communication including industry, production, labour, trade, transportation and even the funerals of victims in numerous countries all over the world (17-22).

The cutback of familiar habits such as participation in restaurant dinners, street demonstrations, cultural and sport events created resistance and distribution of faked information in parts of the society, which, again, raised the hazardous impact of the pandemic (19, 23, 24).

Having these facts in mind the goal of this article focuses on the virtual and real boundaries between the different compartments of affected biological systems, their systemic order, and the consequences of damage, interruption, and reduction of social life. In addition, strategies are described how to repair weakened compartments and how to forecast the development of lockdowns.

Orders of structures in biological living systems

Basic relations, coordinates and definitions

Life is bound to a space of fixed regulations which include three reversible (space) and one irreversible (time) descriptive coordinates. The space contains spatially distinguishable events which can be recognized by one or several observers within a certain observation period (25).

An event is called a structure if it remains fixed or displays with no changes of its boundaries, appearance or localization during the observation period.

If changes occur or if the result of spatial differentiation at different observation times differs from zero it is called a function. Functions can be transformed in structures if

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the period of observation is shortened or if the spatial differentiation results in a new representation space (26, 27) .The situation is demonstrated in <Figure 1>:

FIGURE 1: RELATIONSHIP BETWEEN STRUCTURE – EVENT TIME – OBSERVATION PERIOD

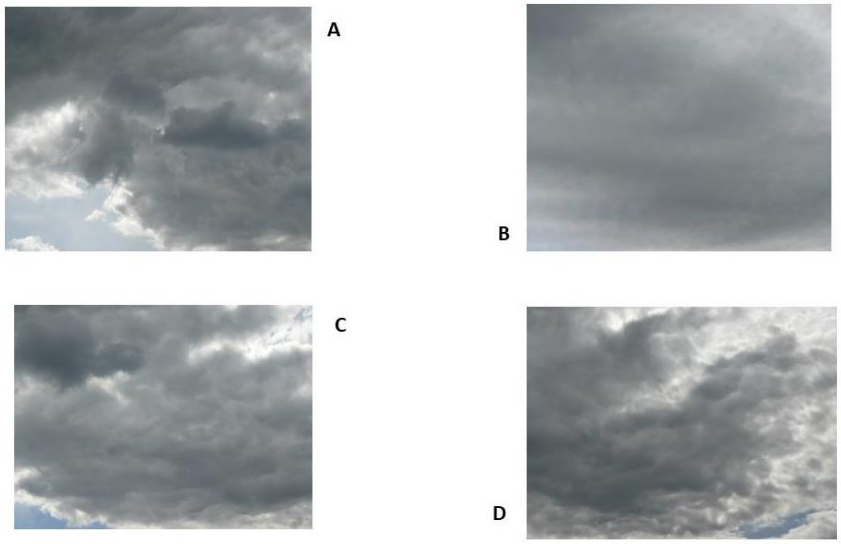

Figure 1: Transformation of an event (cloud) by different observation periods. The example shows a cloud configuration, i.e. transformed structure by short (10 milliseconds) observation period: (A: at start of observation; B: at end of observation; D: cloud structure after 60 minutes. Total of 20 observations within 120 minutes, each observation at an interval of 6 minutes); and transformed by long observation period (C: observation period equal to event time).

and explained from another point of view in <Table 1>.

Orders of Structure

Structures might be spatially open or closed. Open structures display with dimensions lower than their embedding space. If structures are closed they separate a space of their own dimension into two compartments, an inner and an outer compartment (plane, space, etc.). (27) .

Objects belong to closed structures. In reality they are located in a three dimensional space. Their boundaries consist of two dimensional planes. They display with specific features within an inner three – dimensional space that is separated from an outer space (background) (26, 28-32) . Closed structures (objects, events) of three

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dimensional space might be arranged in sets of two different positions, namely of parallel (outer) or of vertical (inner) neighbourhood (27).

Parallel neighbourhood implies boundary connections at the surface only, whereas vertical neighbourhood displays with inner (and outer) positions and surfaces. Horizontal objects can be reduced to and arranged by a two dimensional translation in contrast to vertical objects which require an additional third dimension if they are allowed to communicate or to exchange energy. They represent thermodynamically open systems (27) .

The additional dimension creates a sequence of objects in a hierarchical order which addresses to the whole system (27). An example of realization in nature is shown in <Figure 2 .

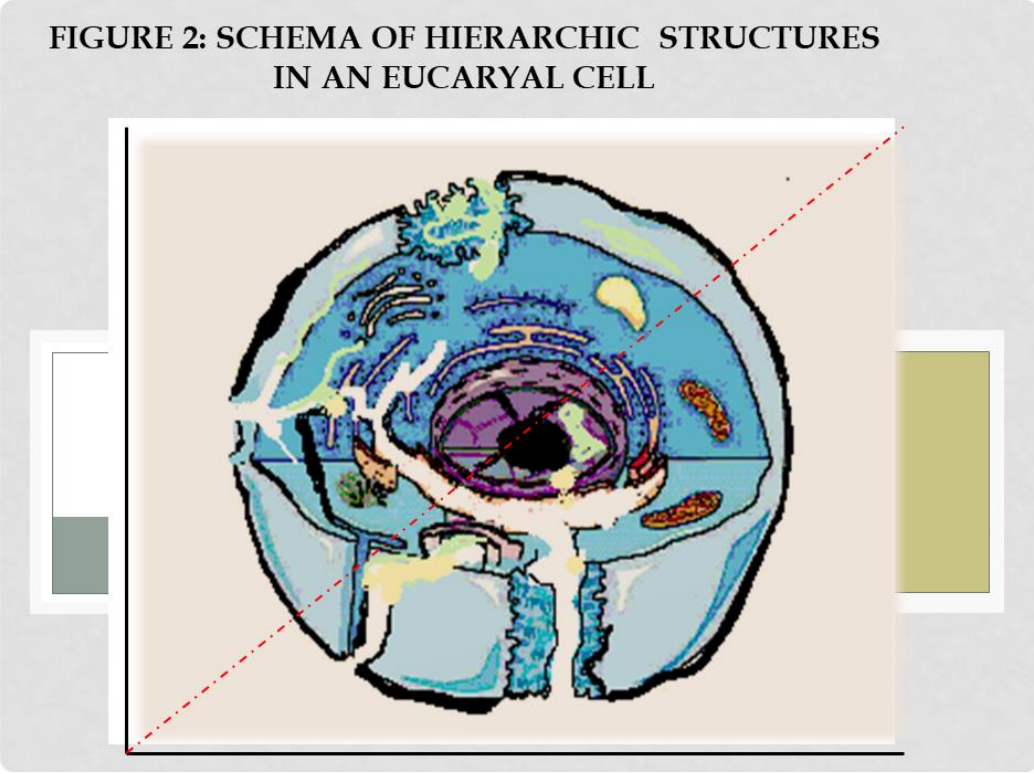

Figure 2: Hierarchic schema of an eukaryal cell: A cellular nucleus is composed of different levels (orders of structures) which contain cellular cytoplasm / nucleolus / mitochondria / membranes / inclusion bodies.

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Algorithms to analyse the system should include the following definitions and methods:

A) Goal of the approach.

B) Neighbourhood condition. (Voronoi's and Dirichlet's tessellation are the most frequently applied procedures (32, 33)).

C) 'Distances' and hierarchy (in a predefined feature space) (29, 30).

D) 'Background' and 'basic units' such as objects, pixels, colours, letters, etc. (34-37).

E) An appropriate mathematical calculation. Herein, graph theory methods with the construction of weighted minimum spanning trees (MST) served for successful application in tissue based diagnosis (30, 35, 38, 39).

F) Application of appropriate statistics, for example multivariate analysis or related calculations such as neural networks (25).

G) Clear separation of potentially associated actions. Herein, the use of reiterative discrimination methods and variable discrimination thresholds are recommended (40, 41).

Such a system has been proven to be successfully applicable in partly or fully automated microscopic image diagnosis, for example in diagnosing various cancer cell types of different organs (26, 39, 40).

The details of the listed prerequisites are: The definition of the approach goal **(A)** serves for the strategy line of the virtual system and the declaration of its limitations without any interaction into its performance. This requisite reflects the separation of legal legislative from the executive.

In image and tissue - based analysis the background defines the space of the system's action and fixes the boundaries of feature range and time allowance. It distinguishes between detectable features (structures, objects, events) and discrimination calculations which are related to the system's future properties (development), i.e. functions of detected structures (26, 40)).

The application of an appropriate neighbourhood condition **(B)** might act on 'independent' space – related properties only (Voronoi, Dirichlet) or on additional conditions such as 'shadow range' of included structures (area of hide), extern or

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internal system – associated features (delay of presence, birth of new or death of existing structures, periods of existence, etc.) (30). Several of these features have been implemented in Jonsohn Mehl or O'Callaghan algorithms (42).

Naturally, distances **(C)** are defined in association with the selected properties that should serve for the system's characterization. Commonly they are predefined by the goal of the approach; for example tumor size, location, and cell type in case of calculation of the patient's survival time (28, 43-45).

The application of graph theory **(D,E)** induces a network of edges and vertices which is exemplarily demonstrated in <Figure <3>.

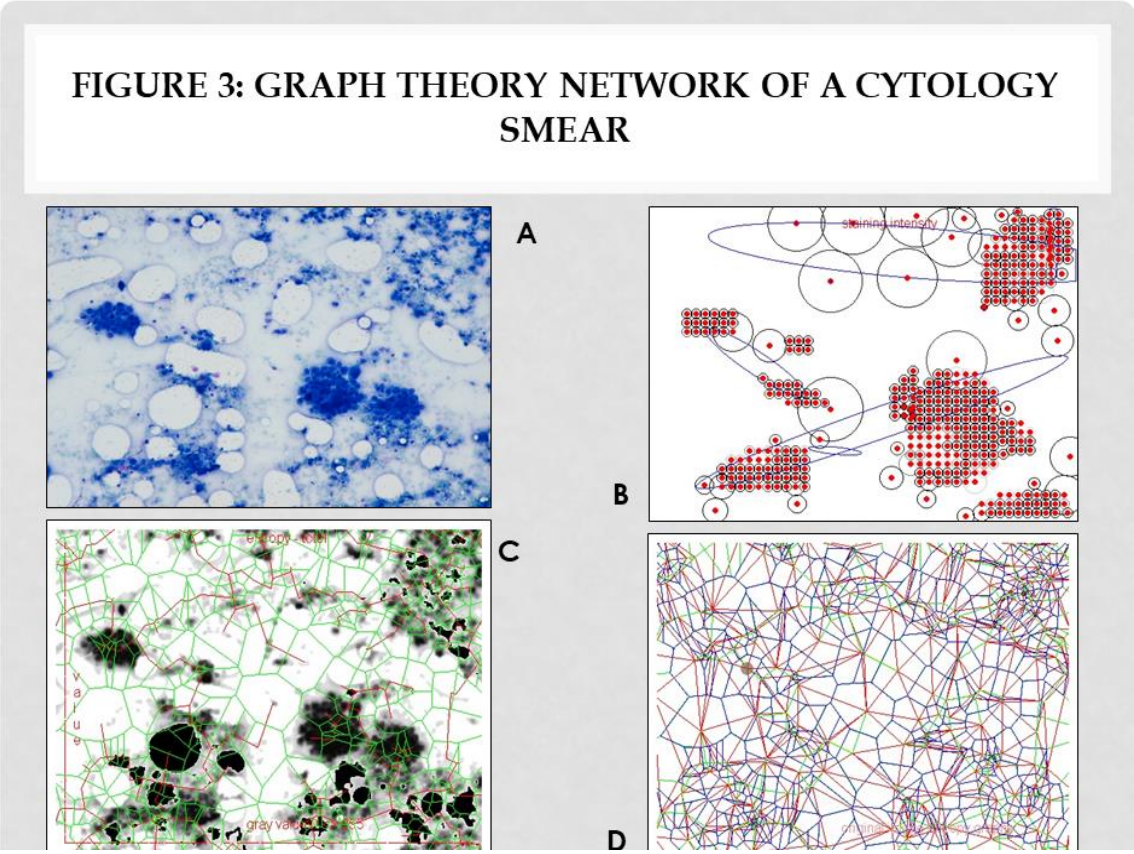

Figure 3: Example of the graph theory network based upon a cytology smear: (A) original image; (B) segmented cells; (C) minimum spanning tree; (D) Entropy network of different clusters .

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Each vertex correlates to a structure and each edge to a realized communication between the vertices (29, 30, 32, 46).

The 'network' stands for a 'higher order' structure which is embedded in and might be separated from the environment (background). It forms the basis of calculations that create the statistical metrics.

The applied statistics **(F,G)** strongly depend on the number of included cases and the number of evaluated features (29, 30, 32, 46). .All frequently applied statistical methods create a 'main stream', separate 'extremes' or rare cases, and classify a new case in relationship to the 'main stream' (47-49). In other words, they predict the fate of an extern case based upon the relationship of its feature expression to that of the totally investigated cohort (50).

The analysis of the investigated cohort remains constant according to its external set up and presumes limitations which are usually independent from the system's feature expression. It becomes more flexible, if recently classified cases are automatically included into the calculation of the next cases. Such an algorithm allows the system to adapt, to grow or to shrink in relation to potential changes of input data during its application (investigation / observation period) (25).

Once such a system integrates and discriminate its calculated results into itself, it automatically builds an additional next 'upper' level of structures, objects or events. The algorithm might start again using the same algorithms or might even alter the previously used neighbourhood detection, applied statistics or discrimination method (25, 27, 31, 51, 52).

The outcome might then tune the data of the preceding first level, and, in addition, search for structures, objects, events of its own level. An approach that included three levels (orders of structure) has been reported to create a flexible, reproducibly stable and promising diagnosis system in tissue – based diagnosis (53-56).

How to derive function from structure?

Recently, it has been shown that biological structures and functions are of the same nature. Their different appearance detectable by human senses depends upon the observation period (25-27). Events appear to be structures if the event's existence (duration time) is long in comparison to the observation period. They display with functions, if the observation period exceeds the event's duration time or if event differences at different observation times can be noted (25-27), <Table 1 and <Figure 1>.

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Differentiation of digital microscopic images is an appropriate technique to deriving potential included (hidden) functions from visible structures (26, 41).

The principle prerequisite of such calculations includes the reversibility of (virtual) time and the validity of the spatial commutative law (26, 41). It is fulfilled in the majority if not in all digitized images (26, 41).

The idea possesses an interesting advantage: It transforms the 'variable' function into a scalar whose parameters can be analysed by natural entities such as entropy models (32, 46). An example of such a functional analysis of intra-cellular structures is given in <Fig. <4>.

Biochemical and social characteristics of the Coronavirus disease

Biochemical data characterize the pandemic Coronavirus disease as follows:

1. Its cause is an infectious virus that possesses a partly reproductive RNA machine which is surrounded by macromolecules. They effectively bind to human cell surfaces and ensure that the RNA can enter the host and use its machine for own reproduction (13).
2. Outside the host, it is bound to droplets from the upper respiratory tract and survives in the air without contact to solid material for approximately 2.74 hours (median), and on plastics for 15.7 hours (median) (3, 57-60).
3. Infection occurs directly by man-to-man transmission (60).
4. Its reproduction period in man lasts for 5 – 10 days (60).

The pandemic influence on social structures includes:

1. The air of human environment can be absolutely controlled only in closed rooms or directly by shelter of the individual persons (60-63).
2. Infected and infectious persons might present without or only with scarce symptoms (15, 17, 64-68).
3. The critical spatial distance between infectious and potentially endangered persons amounts to approximately 90 centimetres (60-63).

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4. Modern societies present with clustered, spatially - and time – associated events such as labour, festivals, sport activities, street demonstrations, etc. which cannot or only partly be controlled by police or government (8, 19, 23, 62, 69).
5. Communication and released actions belong to the most important features of human life. The government regulates them by legal regulations. The rules act like virtual boundaries and separate the 'individual space' from that of its constantly or accidentally existing neighbours (17, 57).
6. Pandemics and fatal catastrophes break the virtual communication boundaries and have been reported to severely damage the involved societies as a whole (20, 70-74). In addition, virtual events and boundaries are prone to age too, might alter by time and break in similar manner as real structures (57).
7. Graph theory approaches and entropy calculations of pandemics investigate in 'social level' virtual events and boundaries. They might be a promising approach to forecast the fate of and to potentially repair Corona - damaged virtual social systems (75, 76).

These statements and considerations seem to be promising and could help to guide human health care interactions, if they are in accordance with the theorems of repair theory at biochemical level (13, 58, 77-80).

However, constraints exist in realization of the proposed idea which include:

1. Delay of mandatory system reaction because of slow signal and communication transfer in and between different society compartments (81).
2. Irreversible breakdown of the system's 'skeleton events' prior to potential repair (58, 80, 82).
3. Feedback and enhancement of infection velocity by repair and consecutive damage of repair mechanisms (58, 80, 82).

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4. Spread of infectious agents in repair tools inside the system and involvement of additional compartments which hinder effective correction (83, 84).

Examples of these constraints are not rare and include antibacterial treatment in combination with mandatory cortisone dose, surgical intervention and poor health condition, or anti-thrombotic therapy and aneurysms.

Laboratory techniques, calculations and algorithms

The complex pandemic corona is a disease entity which involves different layers of structures.

The principle diagnosis should (and does) clearly identify the infectious agent and exclude diseases with similar clinical presentation or virus of similar structure and function (58, 82).

Different Corona test procedures are available and include nested PCR sequencing of the virus genome compartments upE and Orf1a within the genes RdRp- and N (13, 61, 85). The sensitivity of the technique was quite low (40 %) in contrast to its specificity (>95%). Smaller test series of the Shen Sen Hospital in Hong Kong reported sensitivity 70% and specificity close to 100% which are in a similar range of radiologic reports (86).

At least two PCR tests in sequence are recommended if the pretesting presents with high specificity and moderate sensitivity. Its data should be confirmed by a second test (87). It is common practice that most of the officially test publications report the daily or weekly counts of individual positive PCR tests independently from final confirmation.

Additional test series search for antibodies and antigen macromolecules of different tissue – bound immune expression (IgE, IgA, etc.) (87). These tests can detect reaction pattern of the host and deliver a rapid result within 15 – 20 minutes (88).

All tests depend upon the infection time. Its median time until notable (clinical) reaction of the host amounts to 5 – 6 days. The COVID-19 virus can be detected in nasal smears already after 3 days.

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Approximately 70 – 80% of positively tested individuals do not present with symptoms. Approximately 5% of them are confronted with severe health problems and approximately 1% of them do not survive (89).

Immunization kits are under development. The protected effect is supposedly about 80 – 90 % for the exposed persons (3, 15).

Thus, the principal live threatening situation of the Corona disease at biochemical level seems to become solved in the near future (57). Constraints would remain at the social level which includes financing and logistics (90).

Independently, the society has to solve the situation that aerosol small droplets pollute the air and transfer highly infectious agents. They infect without symptoms many persons who become disease carriers for a non - negligible period and who might suffer from late hazards after years (91).

The 'isolation' of the droplets and infectious persons from the potential recipients remains the principal problem. The outstanding majority of potentially virus infectious persons cannot be detected and isolated. The infectious agents cannot be eliminated from the air in general. The air cannot be sealed outside closed spaces and the recipients cannot be isolated from communication and movement.

To make it worse, the members of the society are adapted to regulations which cannot be changed easily. Promised 'freedom' and expected 'fun' diminish caution and distance, and promote the distribution of the hazardous droplets (19, 23, 24, 74).

A rapid and complete lock of the 'open' communicative boundaries would delete the connection (support) of the lower level events (civilians) who 'constitute' the regulative government which is located in the neighbouring upper level.

The described Corona situation includes at least six hierarchically (vertically) levels of (structure / objects / events), namely (1) macromolecule, (2) virus, (3) cell, (4) organ, (5) person, (6) society.

The levels of order host distinct well-defined units which can be described by associated limited features. The situation fulfils the prerequisite that common statistical calculations and the concept of entropy can be applied (31, 41, 46, 52, 92, 93).

The computational algorithm might be arranged according to the procedure reported by Kayser et al (31, 32, 35). This procedure calculates the entropy of the objects / events and the entropy flow in each level. The corresponding entropies between

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nearest neighbouring levels are computed and add to the final result (94-96). An example of the procedure and the results of a crude probability calculation are depicted in <Figure 4>.

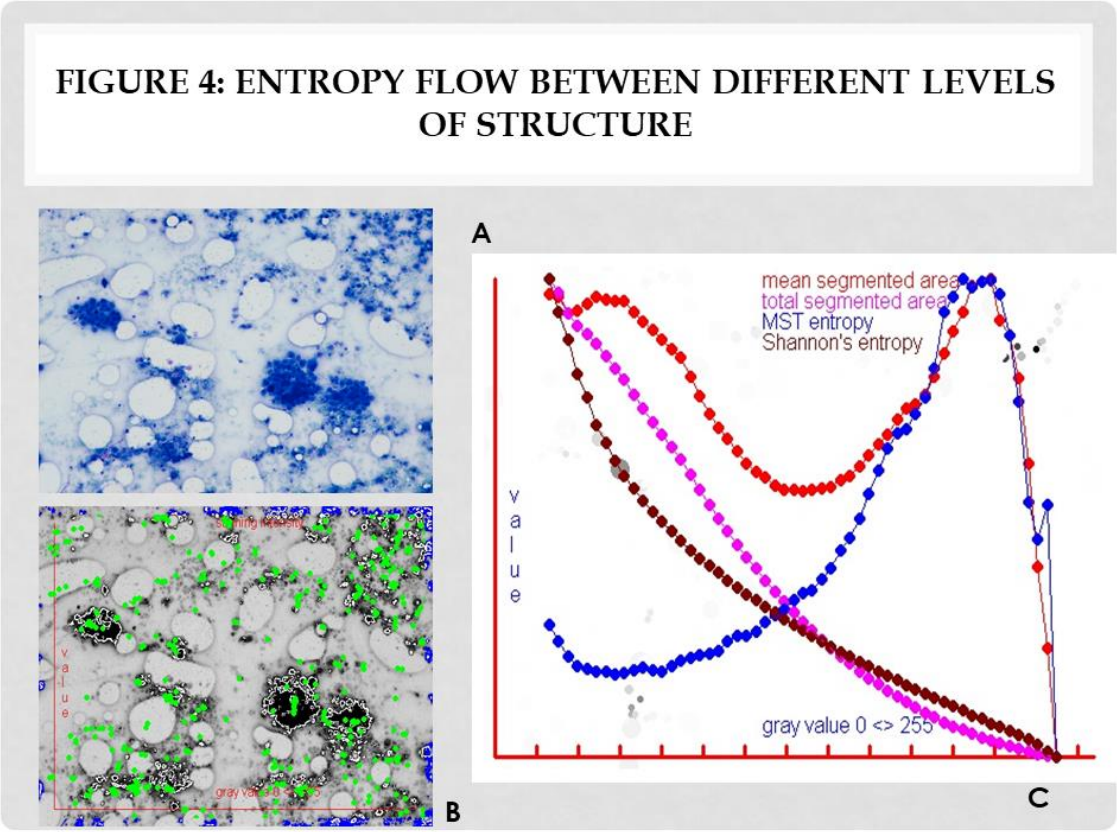

Figure 4: Entropy flow between different levels of structure in microscopic image indicating the functional dynamics of a functional microscopic stain (A) original; (B) Cells and cellular clusters; (C) entropy flow curves calculated for stained areas, structural and Shannon's entropy].

The amount of entropy and entropy flow indicates that the stability and potential damage of measured events can change between different levels of structure and indicate the dynamics of connections (communication) between the different structures (35, 41).

Consecutives and derivatives for the involved societies

Corona is more than a disease at a biochemical level (reproductive RNA macromolecule). It possesses a direct impact on 'higher order structures' and endangers in reality societies and states.

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The presented theory can explain the reason and give advices how to avoid or to minimize the damage. In addition to biochemical protection (immunization of potentially exposed persons) the involved societies are forced to 'immunize' their laws of communication and life regulations in order to limit or avoid serious consequences.

These include:

1. To set up a clear goal of the societies' future development.
2. To redefine the actual definition of 'freedom', 'democracy' and 'equality' (social justice) in Western and Asian States and that of 'belief' in Muslim Countries.
3. To avoid 'belief' in society regulations and to replace it by 'understanding' and 'rationality'.
4. To develop consistent society analysis and repair mechanisms to re-adjust regulations and laws.
5. To support the balance of industrial, financial and legal decisions by statistical multivariate and forecasting analyses.
6. To seriously consider the limits of resources and to adjust equilibrium between 'birth rate' (growth) and 'death rate' (shrinkage) of all significant compartments (population, transport, food, energy, health, sciences, ethics, etc.).

In practice, these changes will imply:

1. A clear definition of 'spaces' which contain the applicable regulations and define their boundaries. Examples are the limits of equality, of freedom, of data protection and of health care. Answers to questions like 'How to select patients who must be excluded from treatment because of limited resources (equality)' should always be answered at the actual date and not in general.
2. A redefinition of ethics and acknowledge of its relationship to essential resources, global catastrophes or different unavoidable events is

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inevitable if the increasing limitations and shortage of resources are seriously kept in mind.

Conclusions:

We are aware that scientists usually stay on the ground of their specific knowledge and avoid statements that go beyond their expertise. However, we feel obliged to describe and discuss the disease Corona 'as a whole' because it can be considered as a 'difficult to handle communication disease' that involves several compartments of human life, from its biochemical ground to its 'heaven of belief' and social structures.

Corona is an example of how densely packed populations and intensive communication are vulnerable to a 'simple' air pollution which was released by a small number of infectious agents (virus droplets) at its beginning.

In addition, it is a disease that demonstrates the limited resources and principal helpless of man, including the only internationally competent worldwide health organization (WHO), whose proposed recommendations, actions and regulations are not taken seriously and simply disregarded by numerous persons and several states.

Corona might be considered the start of nature's unchangeable lessons that strongly direct life style and human survival. Therefore, their lessons should be learned by everybody.

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Klaus Kayser; diagnostic pathology 2020, 6:280
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Table 1 : Definitions of events, structures and functions

Event	- can be observed by one or several observers - occur, depending on period of observation and the resolution of details during any observation **structures** or as **functions**,
Structure	- fixed boundaries - identical appearance - identical location and orientation in space - can be open or closed
Object	Any closed structures in thee dimensional space (e.g. a macromolecule, a nucleus, a cell, an organ, an individual person.
Function	If during observation time any changes occur to a given structure this event is called a function

Comment: **Events** are more likely to be observed as **structures**, if the observation time is short compared to the total time of existence of the **event,** like a snapshot .

Somehow a **function** can be understand like as a roll of analog movie film, which contains this snapshot single frame (**structure**) one after each other. Observing this film at a given frame rate shows up as a **function**.

Depending on the frame rate and the speed, within changes occur the a small snippet of this film might display a part of this function again as a **structure.**