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Unitary Symmetry of Combinatorial Molecules and Mixtures. Part 1: The New Pharmacology as a Valuable Tool in Drug Discovery

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Abstract: Atoms and molecules are the classical discrete combinatorial objects. Thus combinatorial operation can be applied to the objects in their steady (equilibrium) state, and when the reagents considered in successive stationary states at each time point during the entire reaction.

Thus combinatorial operations imply a stationary version combinable initial set of elements - both in the presence of an immutable "core", and so in its absence.

Combinatorial operation in kinetic variant are sequential combination of reagents parts which are practically in the same condition of the different initial objects (without considering the critical temperature and pressure).

Sets of molecules and radicals, appears as a result of combinations of ligands will be called combinatorial molecules. In these cases, the discreteness is given by discrete nature of the ligands.

But discrete objects can be created artificially, representing different pure substances in the form of the set of identical fractions. By mixing such substances in various proportions can be obtained the combinatorial mixture of substances.

The main feature of combinatorial objects is their natural alignment in cross-homologous series. This property of the combinatorial objects allows to obtain self-consistent, most reliable values of the physical (chemical, biological, ...) parameter.

The main feature of chemical entities is the existence of the interactions' hierarchy between nuclei and electrons. between the internal and the valence electrons, between the electron cloud of constant core and the electron cloud of the variable ligand**.**

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These two features allow us to hope that we can choose the ratios of combinatorial objects, in which the strong interactions are fully compensated and for weak interactions these ratios for certain homologies are the invariants of Unitary Symmetry of combinatorial molecules and mixtures [1,2,3]. Thus for a selected class of combinatorial molecules (or mixtures of) these invariants are a system of equations.

And these ratios were found.

The main feature of these invariants is the possibility to calculate the value of a physical parameter for the entire set of combinatorial objects **only on a small number of experimental data, i.e. predict.**

And by this property combinatorial analysis on the basis of a unitary symmetry of chemical entities differs by high throughput research [4].

The features of combinatorial objects discussed in this article as an annex to the main pharmacological Task, which consists in the selection of unchangeable as the "core", and in the selection of ligands. In practice, this problem consists of several subtasks [5]. Once researchers identify promising compound for development, they analyze and conduct experiments in order to collect information on:

- How it is absorbed, distributed, metabolized, and excreted
- Its potential benefits and mechanisms of action
- The best dosage
- The best way to give the drug (such as by mouth or injection)
- Side effects (often referred to as toxicity)
- How it affects different groups of people (such as by gender, race, or ethnicity) differently
- How it interacts with other drugs and treatments
- Its effectiveness as compared with similar drugs

And almost on each of these stages the Unitary symmetry of the combinatorial chemical entities can increase the efficiency of solving the problems listed above.

1. Introduction. New Paradigm

Nature is very "laconic" and "conservative" in its basic Paradigm: **a set of basic elements - a combination - selection** (natural, depending on environmental conditions and man-stimulated by human) **of the resulting combinations**. This three-tier chain is repeated at every level of matter: elementary particles, nucleus, atoms (nucleus + electrons), the molecules (atoms family), codons (a family of nitrogenous bases), proteins (the family of amino acid residues) ...

Next "conservatism" is the level of evolution - or the serial replacement of one element of the initial set of combinable elements to another **of the same set**, or connection to one of the compounds of one-level elements **of the other set** of initial elements from the other level of evolution of matter.

An example for the first case: the formation of a proton and neutron of quarks (.....) *, the formation of multiple nuclei of a proton and a neutron combinations with repetitions, (.....) **, the formation of a combination of molecules with repetitions and permutations of atoms, (.....) ***, polymer formation of combinations with repetitions and permutations of relatively simple molecules ...

Examples of the second case: (.....) * - the formation of different classes of elementary particles when attached to the proton of any of the quarks, (.....) ** - the formation of variety of atoms from adhering to one of the combinations of protons and neutrons (the level of nuclei) a certain number of electrons (elementary particle level), (.....) *** - the formation of complex molecules by replacing one of the atoms in its composition by a group of atoms (simple molecules) ...

In this case, at each stage of evolutionary changes can reveal the sequence of states (objects), when the next state (the object) is different from the previous one by **only one element**. This sequence is what I call **true homological series**. The homology has great predictive potential. In the last century it was underdeveloped - at the level of interpolation and extrapolation. Discovery of Unitary symmetry radically change its predictive capabilities - up to the heights of parallelism in the comparative analysis of the objects and processes of the different levels of evolution of matter

Next "conservatism" - is being shared by all of combinatorial objects hierarchy energy particle interactions, which is composed of a combinatorial object. The existence of a hierarchy allows us in certain cases to neglect the weak interactions and build the physical model only in the approximation of strong interactions. At the same time for atoms and the preferred class of molecules we can try to find such groups of the values the parameter in question, in which the contribution of the "weak" interactions are compensated or negligible.

In elementary particle theory the concept of symmetry and related ideas about the hierarchy of interactions plays a fundamental role [6]. So the relative smallness of the electromagnetic and weak interactions as compared to the strong interaction of nucleons in the nucleus can be considered as a model of the nucleus in the limit of exact symmetry of the strong interactions. In this model, protons and neutrons are physically indistinguishable states of the nucleon and the properties of the nucleus - invariant under isotopic transformations. In the case of atoms and molecules we can also talk about the hierarchy of interactions involved in their formation.

As an example, a "strong" interaction in this case we can point to chemical energy, which is 1-2 orders of magnitude more than energy non-bonded interactions. Another example - when the energy of the valence interactions is much higher than the energy of intermolecular bonds in a in mixtures.

Usually accounting of weak interactions in the 'chemistry is carried out by introducing into physical models of various disturbances. These disturbances typically are unmeasured parameters that are essentially the adjustable values.

Thus, **the present age is the age of a** change of research paradigm (finding the relationship between different levels of evolution of matter), and rapid application of the fundamental laws of New Paradigm in chemistry, biology, genetics, and their derivatives.

XXI century is the century of interdisciplinary knowledge.

The main steps the New Paradigm are:

- selection of the initial elements
- combinations thereof (with repetition, with permutations ...)
- selection of combinations applied on a set of features (ionization energy, dielectric constant, solubility, biological activity, ...)
- detection of invariants relationship between selected combinations to their classification (search Symmetries in space applications traits), evaluation of the reliability of the experimental data for the selected combinations (by finding self-consistent set of values on the homology various combinations of by changing the ligand).
- prediction of many new importants combinations based on a small number of experimental values (by Symmetries invariants system solutions in the area of applied features).

So, why "Unitary Symmetry"? Because it's natural, simple, efficient, and predictive.

2. Introduction to the Theory of Unitary Symmetry. Geometric Symmetry and Unitary (Parametric) Symmetry

A geometric shape of the object is symmetric **if it can be divided into two or more identical pieces** that are arranged in an organized fashion. This means that an object is symmetric if **there is a geometrical transformation** that moves individual pieces of **the object but doesn't change the overall shape** [7].

The simplest example of the geometric symmetry this is shape retention upon reflection of one half of the object in the plane.

The **conservation law of the <u>form</u> of the object** "A" for the case of reflection in the plane is:

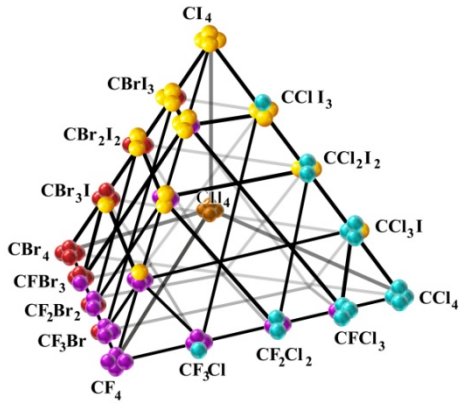
$$A_i(\mathbf{x_i, y_i, z_i}) - A_p(0,0,0) = A_p(0,0,0) - A_i(\mathbf{-x_i, -y_i, -z_i})$$

The symmetry in geometric space implies that:

- it is considered a single object
- no physical fields that could affect the shape of the object
- symmetry is manifested in keeping the shape of the object at different movements of the object as a whole in the space of geometric coordinates (+ time)
- invariants have to be completely accurate

But there is another option of creating (finding) objects consisting of pieces that are arranged in an organized fashion. The truth is that **these "pieces" are not absolutely identical**.

The object on which we will discover a unitary symmetry represents the entire class of molecules, for example, halogenated methane. In our case, a group of halogenated methane can be regarded as a kind of **Hyperobject**. (see Figure 1 and Figure 2).



Five "ligands" (H,F,Br,I) with the same outer electron shell located around some unchangeable "molecular core"

Fig. 1 shows the entire combinatorial set of compounds with the general formula $Y_oH_jF_kCl_mBr_nI_p$, where Y_o - subgroup carbon atoms, or other complex atomic structure.

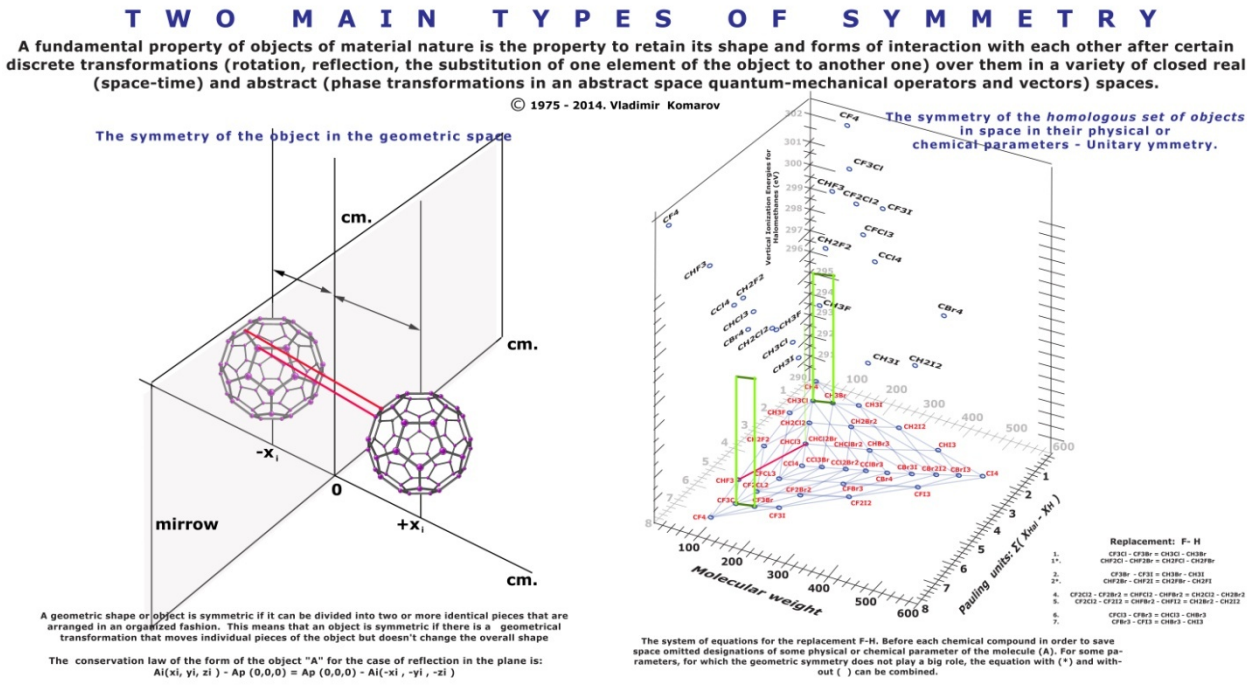


Fig. 2. In the case of geometric symmetry, object (a geometric shape) is regarded as something consisting of multiple (same or different) pieces (left). Object is symmetric if there is a geometrical transformation that moves every individual pieces of the object but does not change the overall shape. In the case of the unitary (parametric) symmetry all combinatorial objects (on the right are not shown) are arranged in this space " I_{VIE} - M - P". They are linked by compensatory ratios (see. right at the bottom; shows 1/10 part). By red color marked symmetric elements of Hyperobject

Considering the **Hyperobject** is no longer in the geometric space, but in the space of its physical or chemical parameters, we can discover a change of its "form".

But it turns out that there are certain constant relation for certain **"parts of the Hyperobject"**

The physical meaning of the constant relations lies in the fact that during the transition from one part of the **"Hyperobject."** (molecules) to another part of the **Hyperobject** strong interaction between electrons and the nucleus are still strong, but with "weak" differing from each other. This difference can be considered as a small correction "± additive" and it can be compensated when finding certain relations for the subgroup of neighboring atoms. (see Table 1).

Table 1. The system of equations for the replacement F-H. Before each chemical compound in order to save space omitted designations of some physical or chemical parameter of the molecule (A). For some parameters, for which the geometric symmetry does not play a big role, the equation with (*) and without ( ) can be combined. The proposed system of equations can be easily transformed to organic compounds (replacing C - CH_3, C_2H_5 ...) or inorganic set (replacing C - Si, Ge, Sn, Pb).

	Replacement: F ⟷ H
1	CF3C1 - CF3Br = CH3C1 - CH3Br
1*	CHF2C1 - CHF2Br = CH2FC1 - CH2FBr
2	CF3Br - CF3I = CH3Br - CH3I
2*	CHF2Br - CHF2I = CH2FBr - CH2FI
3	CF3C1 - CF3I = CH3C1 - CH3I
3*	CHF2C1 - CHF2I = CH2FC1 - CH2FI
4	CF2C12 - CF2Br2 = CHFC12 - CHFBr2 = CH2C12 - CH2Br2
5	CF2C12 - CF2I2 = CHFC12 - CHFI2 = CH2C12 - CH2I2
6	CF2Br2 - CF2I2 = CHFBr2 - CHFI2 = CH2Br2 - CH2I2
7	CFC13 - CFBr3 = CHC13 - CHBr3
8	CFBr3 - CFI3 = CHBr3 - CHI3
9	CFI3 - CFC13 = CHI3 - CHC13

For the entire class of halogenated methanes $CH_{4-n-m}\,X_n\,Y_m$ (X,Y = F,Cl,Br,I) in accordance with the combinatorial substituting one atom to another for combinations ($^{n-1}C_{n+k-1} = (n+k-1)!\,/\,k!(n-1)!$, where n = 5, k = 4 - "n choose k") can be obtained the total amount of replacements (10): F - H, F - Cl, F - Br, F - I, Cl - H, Cl - Br, Cl - I, Br - H, Br - I, I - H. The total number of basic equations is 90.

The main advantage of such invariants is that:

1. All physical property values for the entire class of these objects can be calculated using **only a few** experimental values

2. The values thus obtained will be **mutually agreed upon:**

3. **Erroneous values are easily identified**, for example, using a graphical representation of "the value of a physical parameter - the mass of the molecule" [9]. For example, the database NIST [8] on the enthalpies contains many false values, even for the simplest molecules (see Fig. 3)

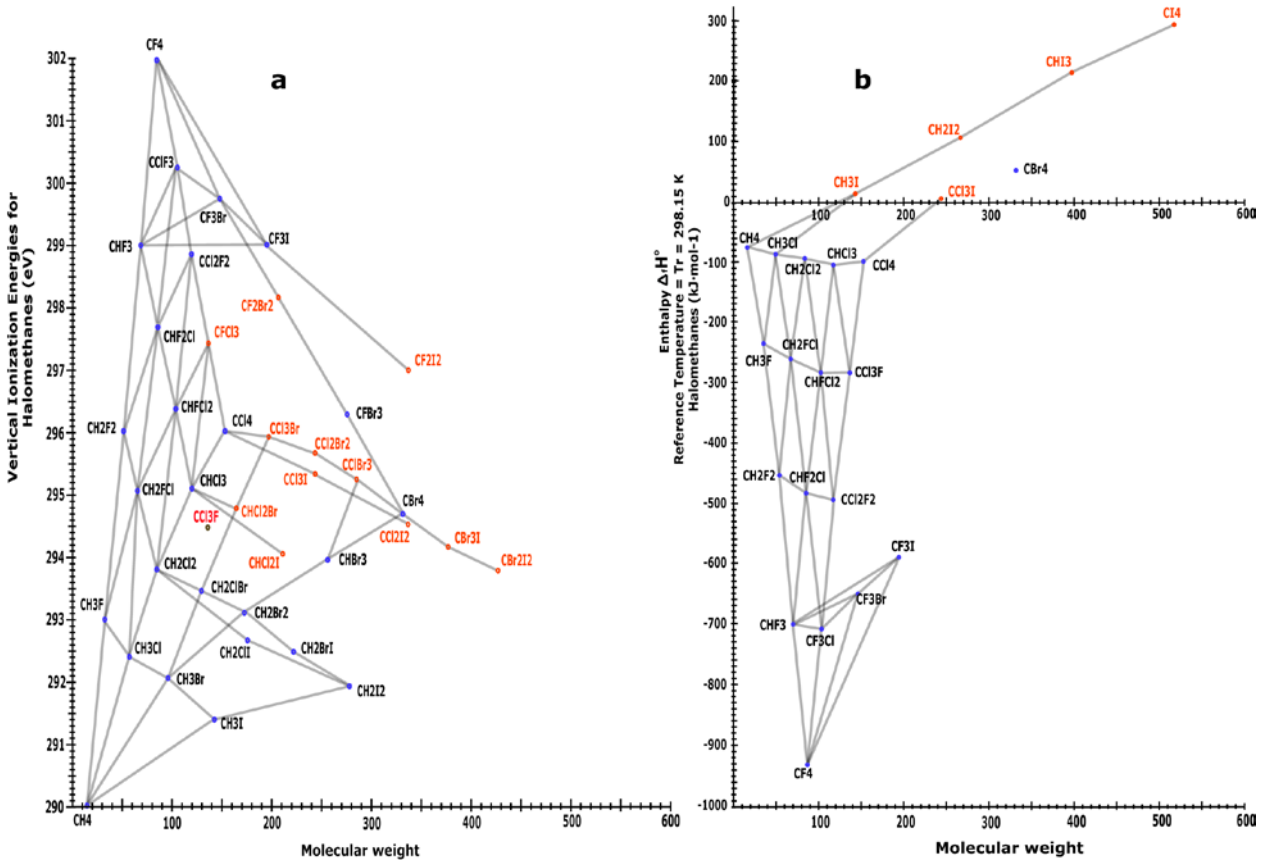


Fig.3. The distribution of halogenated methane in the spaces of their physical-chemical parameters "1S ionization energy of the electron of carbon atom C (I_{VIE}) - weight molecules" (Fig.3a) and "enthalpy of formation of molecules - molecular mass" (Fig.3b).

Fig. 3a. Black letters and blue dots indicate the compounds listed in [9] (for I_{VIE}). Orange color compounds and their values (VIE), the resulting calculations similar to those of Table 1. Red marked compound CFCl3, which in [9] is erroneous. Orange color indicates the calculated values similar to those of Table 1.

Fig. 3b. Black letters and blue dots indicate ΔH_f^o for compounds listed in [8]. Orange color compounds and their values is the resulting calculations of ΔH_f^o [10]. The value ΔH_f^o (ClCl3) is the result of calculations similar to those of Table 1.

So the symmetry in the space of physical parameters of the objects (unitary symmetry) means that:

- it is considered a set of objects formed by one or more combinatorial operations over a number of homologous elements
- the original elements and the final formation of which are dealt with under the force fields and the corresponding hierarchy of energy interactions between all the elements of objects.

- symmetry is manifest in the form of conservation of certain relationships between combinatorial objects if we replace one element of the original homologous series ("ligand") to another member of the same series.
- invariants are approximate, but almost always more accurate in comparison with the experimentally measured.

The physical meaning of unitary symmetry of combinatorial molecules and mixtures is summarized in **Fig. 4.**

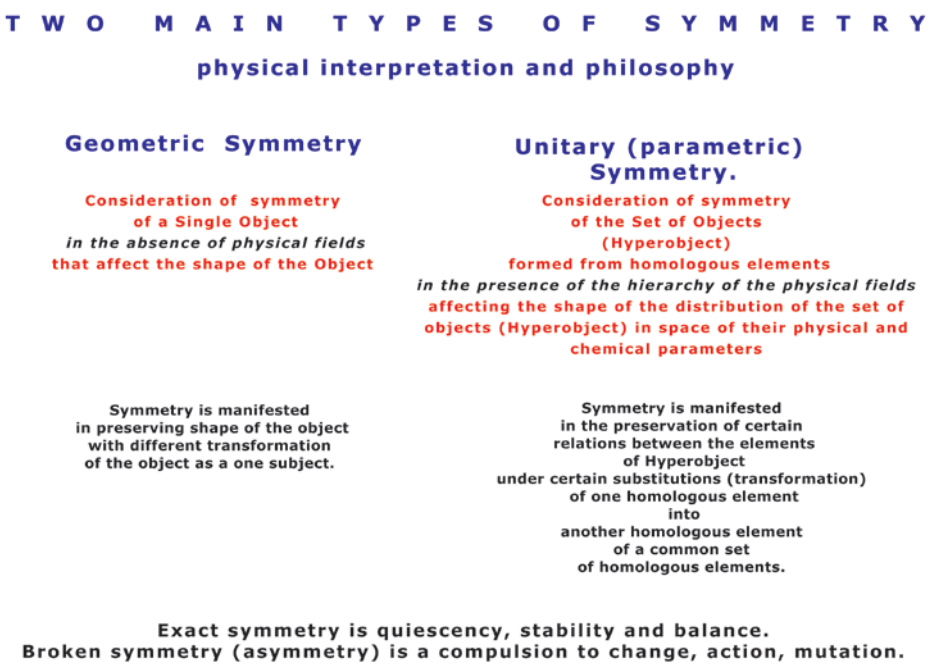


Fig.4. Physical interpretation and philosophy of Symmetry

Figure 5 presents Combinatorial Paradigm Evolution of discrete objects.

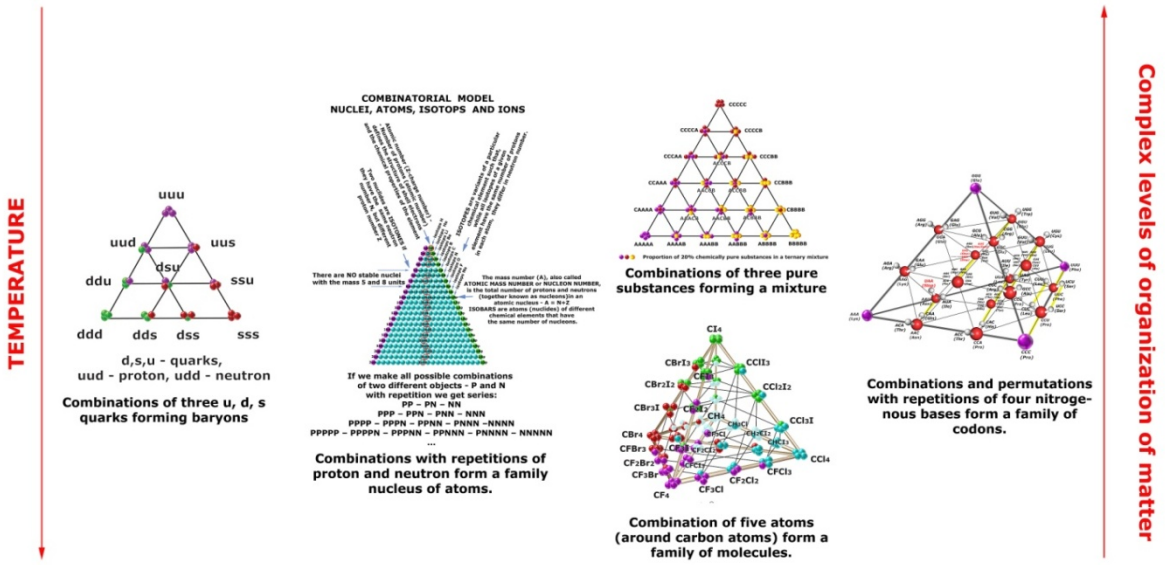


Fig.5. Combinatorial Paradigm of Evolution of discrete objects

Theoretical basis of Unitary (Parametric) Symmetry. is presented in the articles [2, 3].

3. Unitary Symmetry of Mixtures

The mixture can be represented as an object of combinatorics as well. In this case, the "discrete objects" will be the proportion of the components (see. Fig. 6).

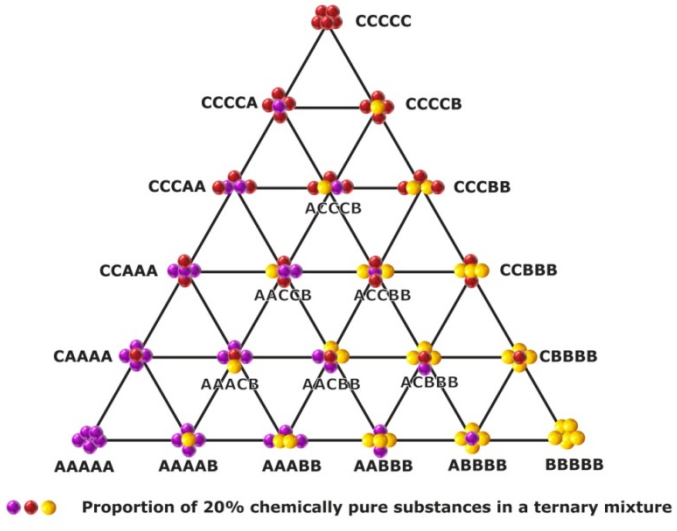


Fig.6. True homologous series a mixture - three different chemically pure substance (A, B, C) in the same phase state, in the same temperature and under constant pressure. Substances are not chemically interact. Shown a mixture with 20% equity step.

Consider two substances A and B. choose a concentration step of 20% of each of these substances. In this case, a mixture thereof can be represented as the homologous series:

A(100%)B(0%)C(0%) - A(80%)B(20%) C(0%) - A(60%)B(40%) C(0%) - A(40%)B(60%) C(0%) - A(20%)B(80%) C(0%) - A(0%)B(100%) C(0%)

The same homologous series can be written for any number of components:

$$A(a\%)B(b\%)C(c\%)D(d\%)E(e\%)...,$$

where (a%)+(b%)+(c%)+(d%)+(e%)...= 100%

Then it is expected that, for example, for a three-component mixture is equality:

$$J(AAACB)_t - J(AACCB)_t = J(AACBB)_t - J(ACCBB)_t$$

where in parentheses are the equivalent fractions of the components, and J - physical or chemical parameter of a mixture of components at a certain point in time. This is the stationary case - the components do not enter into any chemical reaction. We simply measure the parameter J for mixtures of different composition in different experiments.

Fig. 7 shows the homology of the system for the five-component mixtures.

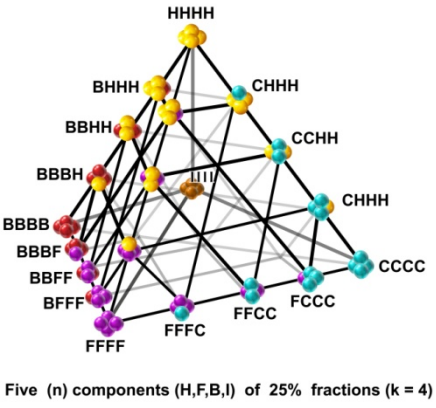


Fig.7. The structure of the homologous series of mixtures The structure of the homologous series turned out to be the weight diagram that corresponds to the irreducible representations of the group SU (5). In order not to overload the graphic not all combinations shown here. Designations of the components - (H, F, B, I) - are chosen specifically to emphasize the commonality with Fig. 1.

The corresponding system of invariants is presented in Table. 2.

Table 2. The system of equations for the replacement of 25% fraction of F component on the same fraction of component H. Before each chemical compound in order to save space omitted designations of some physical or chemical parameter of the mixtures.

Replacement F ----- H	
1	**FFFC - FFFB = HHHC - HHHB**
2	**HFFC - HFFB = HHFC - HHFB**
3	**FFFB - FFFI = HHHB - HHHI**
4	**HFFB - HFFI = HHFB - HHFI**
5	**FFFC - FFFI = HHHC - HHHI**
6	**FFCC - FFBB = HFCC - HFBB = HHCC - HHBB**
7	**FFCC - FFII = HFCC - HFII = HHCC - HHII**
8	**FFCC - FFII = HFBB - HFII = HHBB - HHII**
9	**FCCC - FBBB = HCCC - HBBB**
10	**FBBB - FIII = HBBB - HIII**
11	**FIII - FCCC = HIII - HCCC**

As to the chemical process, the reactants can be represented as a curved line in a certain system homology components This opens up the possibility of describing the chemical reactions in the paradigm of combinatorics.

As emphasized earlier:

1. All physical property values for the entire class of комбинаторных смесей can be calculated using **only a few** experimental values

2. The values thus obtained will be **mutually agreed upon**

3. **Erroneous values are easily identified,** thanks to the self-consistency (mutual intersection) homologous series.

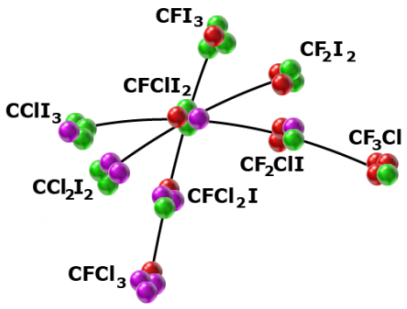


Fig.8. An example of symmetrical self-consistency for the physical parameter of the molecule $CFClI_2$

4. Unitary Symmetry of Hormones' Mixtures. "Hormonal Passport"

The fauna exists in two main hypostases - metabolism and homeostasis in the form of processing all coming from the outside and remove not recycled to save the biochemical balance in the body.

And the metabolism and homeostasis of an animal depends on a combination of age and sex hormones. In humans, this dependence is especially pronounced in the manifestation of secondary sexual characteristics and corresponding physiology and psychology. Therefore, before the "cure" a person need to determine that a person is in a "norm", i.e. to start to solve the problem of "key - lock" - we need to determine a specific pharmaceutical drug appropriate to metabolism and homeostasis of a particular organism.

The first step is to identify the organism in the coordinate system "age - a combination of hormones" (ACH).

At the second stage the resulting index (ACH) should be associated with a combination of hormones secreted by certain glands. The data for the "normal" people would have been a combinatorial representation of a person for the subsequent determination of the necessity and (or) the sufficiency of the application to the patient required medical exposure.

Both of these stages can be combined into a combinatorial representation of the human body problem, which can be called "Hormonal passport"

In general terms, it would seem, "Hormonal passport" would have to look like a solution to the problem **"a particular age - specific composition of the mixture of hormones - ACMH"** for each of 32 glands, for each ethnic group.

With age, everything is clear. How to determine the specific composition of the mixture of sex hormones for the individual is also known. But billions of potential patients! We would like to use a few experimental

data to obtain the maximum number of "Hormonal passports". Under each of which could be pre-pick pharmaceutical drug, its form and dose.

In other words, when referring a patient to a doctor, he would be ready immediately able to identify the patient and offer him the pharmaceutical drug and form appropriate to his "hormonal passport" for a particular disease (which, in turn, is determined by the combinatorial composition of the mixture 57 hormones in the blood, lymph and urine).

Combinatorial problem in this case, it would seem, it is simple: for each of the 32 glands make up a combination of hormones for 18 .... How many? On 2, 3, 4, ... with repetition or not? Extensive task. As a method of high throughput research [4]

Dead end?

No! Comes to the aid parallelism with atomic nuclei [11]. Combinations of two nucleons - protons and neutrons with repetitions gives us a clear picture that the number of repetitions are limited. (see Fig.8.). It is enough to try to synthesize isotopes with a large number of neutrons (isotopes), or protons (isotons) than 3 and make sure that such nuclei decay rapidly.

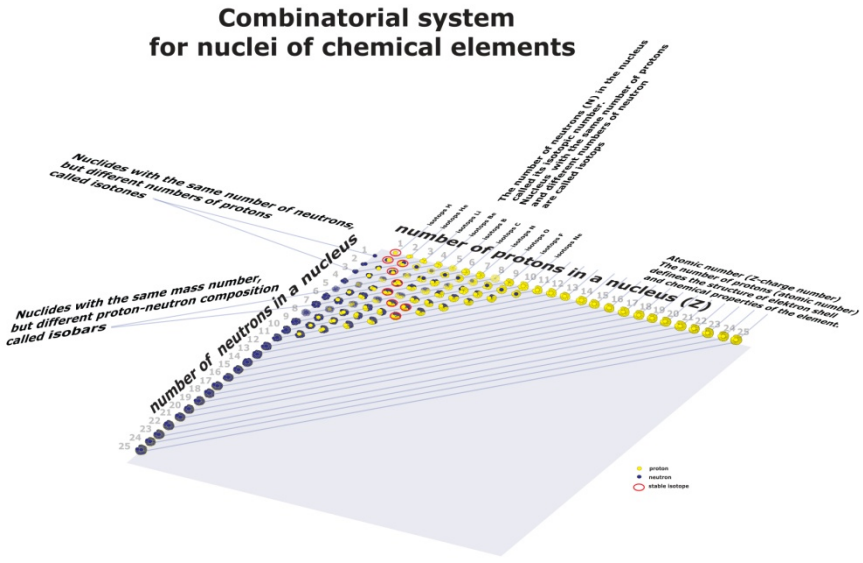


Fig.8. Combinatorial nuclei system of chemical elements

Also, should do in the case of hormones (see. Fig. 9). We are examining some Task Team for the composition of sex hormones in the absence of Pathogens (Norm). We determine the composition of the natural variations of repetitions hormone fragments, for example, for a hundred subjects in a single genotype

ethnos. Next, take the number of repetitions as the basis for finding all the possible varieties of hormones fragments of compositions by solving a system of invariants of unitary symmetry of mixtures. (as by invariants in Table 1).

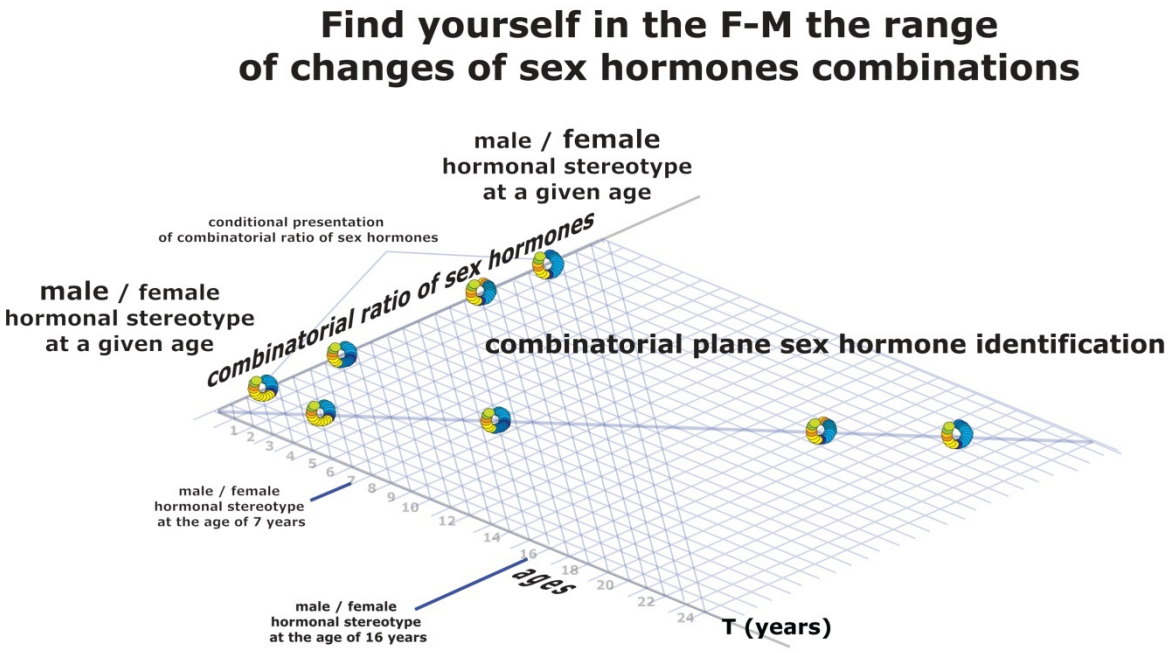


Fig.9. Identification of the person (patient) in the paradigm of "age - a combination of hormones"

Excess male or female sex hormones in the mixture indicates either a genetic disorder of the equilibrium composition of the sex hormones to a certain ethnic group, or of a serious disease of sex glands.

So the limitation of "repetition" of the same hormones in the mixtures determine the "norm" for every age, i.e, construct a "normal line" (straight or curved, as in the case of the nuclei of atoms).

But that's not all advantages of "Hormone passports". Parallelism [11] with a combination of nucleons, where interesting patterns invariant for observed the mirror nuclei (see Fig 10) allows us to hope to find similar invariants and for the so-called "mirror mixtures", ie when, for example, for the two fragment compositions may be just and equitable relationship:

$$J[M (30\%A, 20\%B)] - J[M(20\%A, 30\%B) = const,$$

where J - some measured physical parameter of mixture, M - a constant component composition, A and B - the components with mirror the composition of fractions.

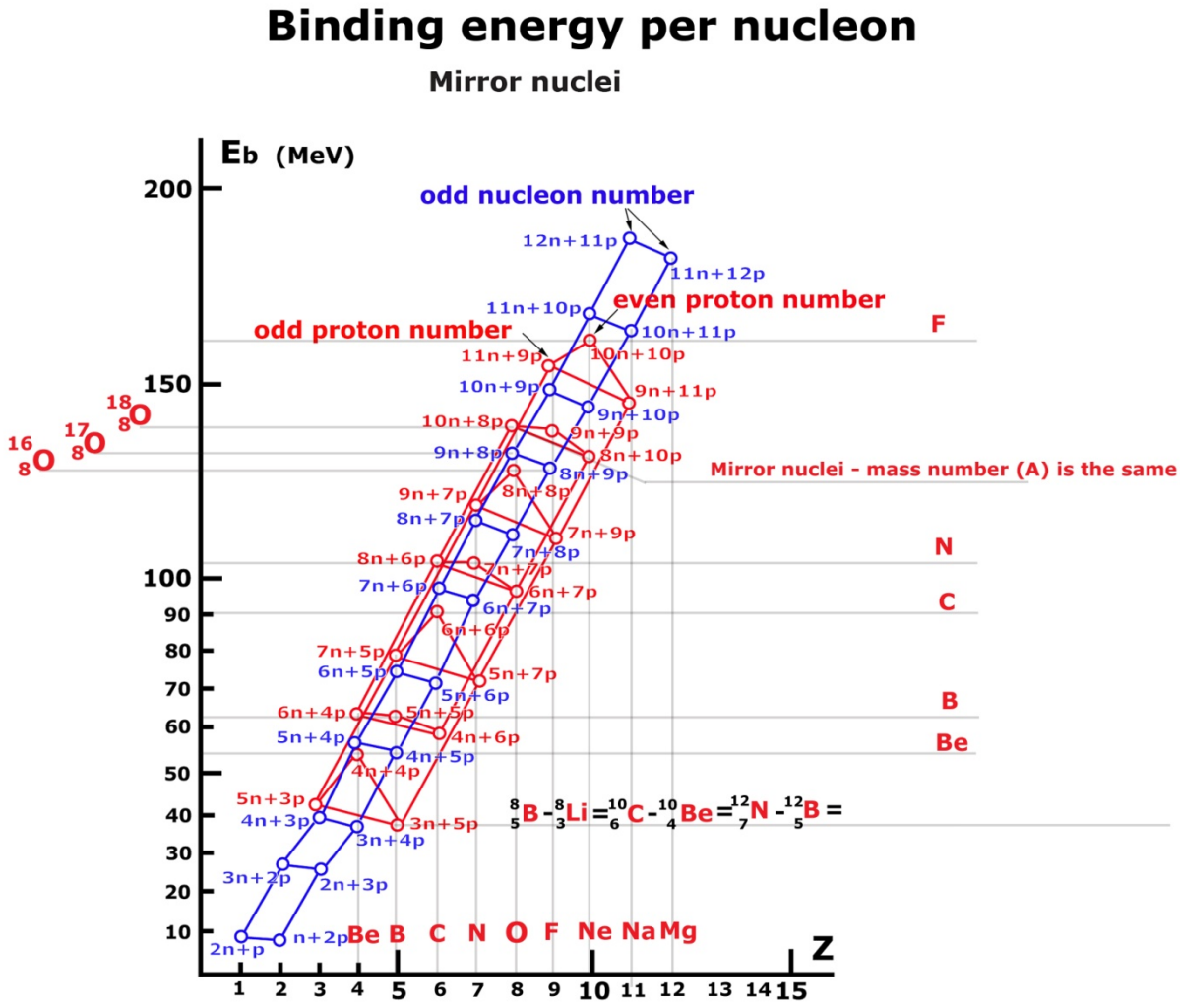


Fig.10. The homology of mirror nuclei. One example of invariants for some mirror nuclei:

$$^{8}_{5}B - ^{8}_{3}Li = ^{10}_{6}C - ^{10}_{4}Be = ^{12}_{7}N - ^{12}_{5}B =$$

Such invariants for combinations of fractions of hormones in the mixture can increase the diagnostic potential of Hormone passport.

5. Unitary Symmetry and Pharmacological/Pharmaceutical Problem

So, the known [5] pharmacological problem is as follows:

1. How the pharmaceutical drugt is absorbed, distributed, metabolized, and excreted
2. What is the potential benefits and mechanisms of action

3. What is the best dosage
4. What is the best way to give the drug (such as by mouth or injection)
5. What is the side effects (often referred to as toxicity)
6. How it affects different groups of people (such as by gender, race, or ethnicity) differently
7. How it interacts with other drugs and treatments
8. What is the effectiveness as compared with similar drugs

It is also known [4] that at the present time, the first step to solve this problem is the prerogative of combinatorial chemistry.

Typically, researchers discover new drugs through [5]:

- New insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease
- Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases
- Existing treatments that have unanticipated effects
- New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material

At this stage in the process, thousands of compounds may be potential candidates for development as a medical treatment. After early testing, however, only a small number of compounds look promising and call for further study.

Even the first step requires considerable efforts of chemists to select a small number of substances that look promising chemical compounds for further research.

In my opinion this first stage could be as follows:

1. select a certain group of subjects **$ACMSH_1$** (with the same or similar values of **"a particular Age - specific Composition of the Mixture of Sex Hormones - ACMSH**) with high immunity to a particular kind of pathogen **P_1.**

This step solve the problem of more accurately determination the characteristics of homeostasis for people who differ in gender identity, race or ethnicity. (See # 6 of. Pharmacological problem).

2. this group is exposed to a pathogen **P_1** (vaccinated subjects)
3. at examinees is measured combinatorial structure and temporal dependence of the combinatorial structure of immunomodulators (natural substances, proteins capable of exerting a controlling effect on the immune system).

This combinatorial structure should be the composition of pharmacological agents (synthetic or composition, extracted from natural objects or living things) to inhibit pathogen P_1. This step is actually solve the first two points of pharmacological problem.

4. select a certain group of subjects **$ACMSH_2$** (with **another** but the same or similar values of **"a particular Age - specific Composition of the Mixture of Sex Hormones - ACMSH**) with high immunity to a particular kind of pathogen **P_1.**
5. repeat the procedure 2 and 3.

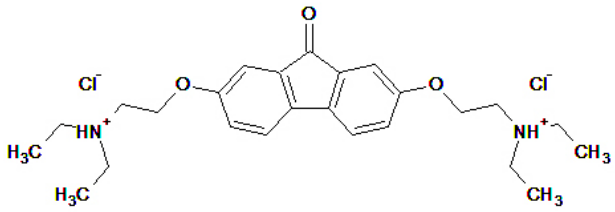
The set of experimental values for $ACMSH_j$ - combinatorial composition of immunomodulators will enable a system of invariants for any composition of immunomodulators and accordingly, any composition pharmacological drugs and their doses (see points # 3 of pharmacological problem).

6. repeat the procedure 1- 5 for pathogen **P_2**

And so on.

For some chemicals may need to find New Stereoisomer form. **Predicting such Multy Stereoisomer compounds are also beyond the scope of unitary symmetry of molecules.**

For some chemicals may need to find **new ligands - homologues**. For example, for such a compound as Tilorone



may be the best in terms of biochemical activity of homologs, where CH_3 replaced by CH_2F group, CHF_2, CF_3 (the example unfounded in terms of Biochemistry). **Prediction of biochemical activity of such compounds are also part of the problem of unitary symmetry of molecules.**

This creates a database for pathogens **P_k** on a variety of patients with different **ACMSH**j.

6. What Happens Next?

Unitary symmetry of combinatorial molecules and mixtures. Part 2: New Medical diagnosis as a combinatorial tool for early prediction of disease.

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