Molecular signalling from the TGD point of view

March 24, 2022

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Abstract

The findings of Elowitz et al lead to a formal model suggesting that ligands of type BMP (bone morphogenetic protein) have interactions. The interactions would be non-local so that it is difficult to imagine that they could have chemical origin. The TGD based model for these long range interactions is based on dark photon resonance. For the simplest, receptors would correspond to fixed bio-harmonies. In a single ligand system the ligand would have the bio-harmony of its preferred receptor. The interaction between ligand magnetic bodies would be re-tuning and could replace the preferred bio-harmonies assignable to the participating ligands with distributions of bio-harmonies. Therefore the ligands of the multi-ligand system would couple by bio-resonance also to other than preferred receptors.

The model stimulates questions, which lead to a rather detailed model for the re-tuning and tuning processes at the level of codons and amino acids. The model suggests that the tuning to a given bioharmony for the dark counterparts of basic biomolecules and its stabilization involves epigenetic control based on the methylation of some special DNA and RNA nucleotides and amino-acids acting as analogs of tuning forks.

The proposal that bioharmonies are molecular correlates for emotions suggests that this process involves minimal number of methylations, which define the seed of phase transition to a bioharmony in the scale of the basic unit of genome (such as gene), mRNA sub-unit (splicing) and protein sub-unit.

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1 Introduction

I learned recently about interesting findings about communications of information molecules. The Quanta Magazine article "*Biologists rethink the logic behind cells molecular signals*" (`https://cutt.ly/iA28lqn`) summarizes the findings of Elowitz et al described in the article "*The context-dependent, combinatorial logic of BMP signaling*" [I3] (`https://cutt.ly/yA8r07b`).

1.1 Observations

Messenger molecules attaching to receptors are thought to be responsible for chemical communications. Intercellular communications would involve first messengers (hormones, neurotransmitters,...) and intracellular communications second transmitters, which are not proteins but rather light molecules.

The standard interpretation has been that messenger molecules themselves define the message. Lock-key hypothesis states that the ligand has a special region (key), which attaches to the receptor in a context independent way determined by the geometries of these regions. Induced-fit hypothesis states that the regions in question can modify their surfaces to achieve a perfect fit. For bacteria only intracellular communications are possible and for them there is evidence that in some special cases lock-and-key principle works as was demonstrated by Michael Elowitz, the leader of the research group behind the recent work.

The findings of the Elowitz and his coworkers force them to conclude that this model fails for the multi-cellulars.

1. The group studied so-called bone morphogenetic proteins (BMP) (`https://cutt.ly/oA7kZna`), which regulate how cells proliferate and differentiate in various tissues by directing them to turn sets of genes on and off. These proteins have many other functions than bone growth.

2. BMPs are so-called 1st messengers and mediate communications between cells. BMPs attach to the receptors of various types at the surface of the cell. This step is followed by signal transduction actinating the corresponding signalling pathway. Eventually this leads to a generation of transcription factors in the cell nucleus controlling the genetic response. The work concentrated on the study of the binding of BMPs to the receptors at the cell membrane.

3. Mammals have genes that encode 11 or more distinct BMP proteins. BMPs occurs dimeres of the same or different proteins and also these pairs can pair up. The family of BMP proteins sticks to the associated family of receptor proteins, which also appear as dimers of pairs of them. BMP molecules are not very selective but given BMP sticks to several dimer pairs of receptors.

Several interesting findings were made.

1. The response of a cell to several ligands is not simply the sum of responses of individual ligands. The lock-key mechanism assuming 1-1 correspondence between ligands and receptors fails in the presence of several ligands whereas for a single ligand there is strongly preferred receptor for a giveng ligand.

The simplest chemical (and thus local) explanation that in presence of several ligands the affinities K_{ijk} of ligands L_i to the receptors R_{jk} formed by dimers (j,k) of homologous or nearly homologous molecules change so that approximate 1-to-1 correspondence becomes 1-to-many. This is called promiscuity.

The responses as concentrations at the cell membrane for the activated signalling pathways P_{ijk} associated with receptor i+jk would be still linear in concentrations of L_i but the matrix characterizing the rate for the creation of P_{ijk} would not be diagonal matrix anymore with respect to pairs (i, jk).

2. This situation is easy to model mathematically but it is difficult to understand the physical mechanism behind the promiscuity.

3. The affinities are context dependent in the sense that they depend on the target cell and the developmental stage of the cell.

4. One can classify the ligands in terms of whether they tend to increase or reduce receptor expression. Ligands can be also classified in terms of their positive, or negative synergies with other ligands. In the simplest situation one studies all possible pairs of ligands and finds their responses. Two ligands L_i and L_i are regarded as equivalent if the responses for the pairs (L_i, L_k) and (L_j, Lk) are identical for all k. This defines functional equivalence. Sequence similarity (biological homology) does not in general reflect the functional equivalence.

   The effects of the ligands in equivalence classes depend on the context (cell type and cell age correlating with receptor concentrations). However, it is found that the equivalence classes are context independent. The proposal is that a single linear parameter could characterize the equivalence classes for BMPs considered.

5. This inspires a chemical model for the situation. The basic parameters would be affinities K_{ijk} telling the tendency of ligand L_i to attach to dimer (j, k), signal complex activities ϵ_{ijk} characterizing the rate for the formation of signal complex P_{ijk}. Also the receptor concentrations A_i and B_i for the receptors of type I and II appear as parameters. The empirical data makes it possible to find the best fit for the parameters. Promiscuity is the basic predictions. The model could be understood in terms of the competition of ligands for receptors (j,k).

   An inverse relationship between affinities and activities is predicted. Small number of affine ligands with weak activity or vice versa.

1.2 TGD view about the findings

What can one say about the situation in the TGD framework? Here only the key ideas of the TGD inspired quantum biology are described. More detailed summaries can be found in various articles related to dark variant of biochemistry [L16, L2, L12], to dark realizations of genetic code [L1, L9, L6, L11, L15], and to the models for cell membrane as generalized Josephson junction [K3, K1, K4] [L10], of Pollack effect [**?**], and of water memory and morphogenesis [K2] [L14].

1. The basic notion is magnetic body (MB) carrying dark matter as $h_{eff} = nh_0$ phases of the ordinary matter and behaving quantum coherently in length scale proportional to h_{eff}. MB would control biomatter.

   Communications to MB, sensory input, would be in terms of generalized dark Josephson radiation from the cell membrane and the control by MB in terms of dark cyclotron radiation. The sensory input would be from the entire cell membrane and induced by the attachment of the ligands to the receptors.

   The earlier proposal was that the control signals from MB affect directly the genome. The existing chemical picture based on signal pathways activated at the cell membrane however suggests that the situation is not so simple. The control signal arrives from MB to the receptors and activates signal pathways. At the nuclear membrane similar processes would occur and lead to the activation of transcription factors by similar signal pathways.

2. If the MB determines the response of receptors in a non-local way, promiscuity could be only effective. Another option is that MB can control the affinities of receptors (by modifying their surface geometries as in the induced fit model) so that the diagonal L-R matrix becomes non-diagonal.

3. Context dependence would conform with the idea that MB determines the response and changes during aging. The aging can be understood in the TGD framework as slow thermalization of MB so that its temperature approaches the Hagedorn temperature of magnetic flux tubes. Physiological temperature would be related very closely to Hagedorn temperature of MB.

The almost computer program-like determinism of biochemistry is in a sharp conflict with the stochasticity expected to result from the locality and statistical nature of chemistry.

1. In the TGD framework and at a given level of scale hierarchy the dynamics of the space-time surface as a preferred extremal is deterministic apart from small violations of determinism. Space-time region as a preferred extremal is a minimal surface with singularities, which would bring in the failure of determinism. Soap film with frames serves as a good analogy.

2. The notion of a magnetic body having flux tubes as body parts leads to a model of bio-catalysis in which molecules are replaced with nodes of flux tube network. Molecules can find each other as part of this dynamical network involving reconnection of U-shaped flux tubes and their shortening in a reduction of h_{eff} liberating energy making to overcome the potential wall making the reaction low.

3. One can argue that the second law implies stochasticity in molecular scales. Zero energy ontology (ZEO) is another possible source of determinism. In so called "big" state function reductions (BSFRs) the arrow of time changes and the time evolution leads to the direction of geometric past so that for the observer with the standard arrow of time the time evolution obeys second law in wrong time direction and looks like self-organization which is basic characteristic of living matter and usually thought to involve metabolic energy feed in an essential manner. In fact the time reversed time evolution would change dissipation as loss of energy with extraction of energy from the environment.

The findings of Elowitz et al [I3] lead to a formal model suggesting that ligands of type BMP have interactions. The interactions would be non-local so that that they could have chemical origin. The TGD based model for these long range interactions is based on dark photon resonance. For the simplest, receptors would correspond to fixed bio-harmonies. In a single ligand system the ligand would have the bio-harmony of its preferred receptor. The nteraction between ligand magnetic bodies would be re-tuning and could replace the preferred bio-harmonies assignable to the participating ligands with distributions of bio-harmonies. Therefore the ligands of the multi-ligand system would couple by bio-resonance also to other than preferred receptors.

The model stimulates questions, which lead to a rather detailed model for the re-tuning and tuning processes at the level of codons and amino acids. The model suggests that the tuning to a given bio-harmony for the dark counterparts of basic biomolecules and its stabilization involves epigenetic control based on the methylation of some special DNA and RNA nucleotides and amino-acids acting as analogs of tuning forks.

The proposal that bioharmonies are molecular correlates for emotions suggests that this process involves minimal number of methylations, which define the seed of phase transition to a bio-harmony in the scale of the basic unit of genome (such as gene), mRNA sub-unit (splicing) and protein sub-unit.

2 Bio-harmony and context dependence

Also bio-harmony might relate to context dependence if fundamental communication and control signals take place at the dark level that is between DAAs instead of AAs (amino acids) as parts of proteins by energy and frequency resonances. DAAs would pair with AAs and communicate with energy resonance.

2.1 Bio-harmony

Consider first the bio-harmony [L1, L6, L9, L15] in more detail.

1. Z_6, Z_4, and $Z_{2,rot}$ or $Z_{2,refl}$ act as symmetry groups for the 3 icosahedral Hamiltonian cycles. Each cycle, one of type XZ_6, one of type Z_4, and one of type Z_2, defines 12-note scale and 20 3-chords identified as icosahedral faces and DNA codons. The notes along the cycle are obtained as a quint cycle, that is by scaling the frequency of the note by factor 3/2 at each edge of the oriented cycle.

   The orbits of faces under Z_n are assigned with amino-acids (AAs). This assumption has a concrete interpretation in terms of resonance mechanism for bio-communications [L15].

   This gives 60 3-chords and the numbers of triangles at the orbits of triangles and the numbers of triangles at orbits correspond nicely to the numbers of DNA codons coding for AAs. 4 codons are however missing. The fusion with a unique tetrahedral code gives 64 chords and a dark 3-photon realization of the genetic code.

   Also the identification of DtRNA, dtRNA, and DAA in terms of icosahedral code is possible as found quite recently [L15]. Also the dark realization of genetic codons in terms of dark proton triplets allows this.

2. Z_6 allows unique icosahedral harmony defined by 12-note scale realized as an icosahedral Hamiltonian cycle. The corresponding AAs correspond to 3 DNA 6-plets and one DNA 2-plet. Z_4 corresponds to 2 bioharmomies with 5 amino-acids which correspond to DNA 4-plets. $Z_{2,rot}$ and $Z_{2,refl}$ correspond to 10 2-plets both. $Z_{2,rot}$ corresponds to 3 icosahedral harmonies and $Z_{2,refl}$ to 5 icosahedral harmonies. This makes $1 \times 2 \times (3+5) = 16$ bio-harmonies if the common key of the 12-note scale for the 3 icosahedral harmonies does not matter and the orientation of the Hamiltonian cycle does not matter. One can also consider the possibility that the key and the orientation of the cycle for the 3 icosahedral harmonies matter. The change of the orientation replaces quint cycle with quart cycle (CG correspond to quint and CF to quart).

3. The interpretation of bioharmonies is as correlates for moods, emotional states. There is evidence for this interpretation from the strange finding that RNA is able to transmit conditioning based on negative or positive emotions generated by stimulus (`https://cutt.ly/6SuLNqk`) discussed in the TGD framework in [L5, L7]. The interpretation would be that DRNA represents the effect of stimulus by its bio-harmony characterizing emotional state, and can induce molecular emotional expression in DDNA-DNA pairing and also in DAA-AA pairing and DX-X pairing in general.

   DX-X pairing by energy resonance mechanism would correspond to emotional expression. Something in X would depend on bio-harmony. In the case of DNA and RNA this something could be the methylation state and its analogs so that there would be a direct connection with epigenesis. Epigenesis would realize the dynamics of emotional expression.

One can raise several questions about bio-harmony.

1. How fast is the dynamics of the molecular and higher level emotions and moods? If epigenetics controls the dynamics of emotions, it could be rather fast at the molecular level. Note that the hierarchy of Planck constants predicts a hierarchy of time scales.

2. How large parts of a given organism a given bio-harmony could characterize? Biomolecules, cell nucleus, cell, organelle, ...? Is there a hierarchy of harmonies so that the harmonies in different scales need not be identical?

   Concerning molecular bio-harmonies, epigenetics could help to answer the question. For instance, one can ask whether bio-harmony characterizes individual bio-molecules such as enzymes and receptors.

3. Could bio-harmony explain at least part of the context dependence found in the ligand-receptor dynamics by the group of? It would seem that bio-harmony appears as an additional aspect of the ligand-receptor pairing involving geometric constraints modelled in terms of

lock-key or induced-fit mechanisms. The enzyme and substrate would be like daters. The resonance mechanism would allow E and S to meet and geometric constraints would determine whether this can lead anywhere.

4. This inspires several questions. Could the affinities and signal complex activities be determined by the molecular emotional state of the L-R composite coded by the bio-harmony of the DX-X complex? Could the "emotional" state DX-X control affect the state of X complex? How? Could this coupling have interpretation as emotional expression in a generalized sense?

5. For the simplest model this would predict that for Z_4 the 5 AAs coded by 4 DNA codons would have two emotional states and for Z_2 10 DAA-AA pairs could have 3 *resp.* 4 emotional states depending on whether one has $Z_{2,rot}$ *resp.* $Z_{2,refl}$.

2.2 Could ligand interactions reduce to a re-tuning of ligand harmonies?

The notion of ligand interaction has been introduced as a purely formal notion in the article and it is difficult to imagine a local chemical realization for it. However, the fact is that ligands change their behavior in the presence of other ligands. Could the ligand interactions be realized at the level of their MBs?

2.2.1 Ligand interactions as re-tuning

Could ligand interactions reduce to the re-tuning of ligand harmonies by the resonant dark photon interactions between DAA flux tubes?

1. Assume that ligands and receptors can have several bio-harmonies but that free ligands (single ligand situation) and in the absence of other ligands they correspond to single preferred bio-harmony. Assume that each receptors corresponds to a single bio-harmony (also this assumption could be relaxed). Free energy minimization could imply preferred bio-harmonies for both receptors and ligands. Assume that ligands can only pair with receptors with the same bio-harmony. The immediate question is whether the 3+4 receptors assigned with BMPs could relate to 3+5 Z_2 type harmonies. The problem is that one $Z_{2,refl}$ harmony would not correspond to a receptor.

2. Interactions between two ligands L_1 and L_2 with different bioharmonies could induce a re-tuning of L_1 to the bio-harmony of L_2 or vice versa. This tuning must respect the symmetry group Z_n, $n = 6, 4, 2$ in question. The Z_n orbits would be preserved but the corresponding 3-chords would be modified.

   Some findings about water memory [L14] support re-tuning as a basic mechanism of communications between dark biomolecules and it is very natural in the resonance picture. Note that re-tuning is a basic mechanism in radio communications.

   Re-tuning would replace the ensemble of ligands with an ensemble in which also non-preferred L-R pairings are possible. It would make the affinity matrix $K_{i(jk)}$ and activity matrix $\epsilon_{i(jk)}$ non-diagonal and induce promiscuity. Probability distribution for bio-harmonies of ligands would emerge in this way.

3. The large-scale quantum coherence at the level of MBs inspires the question whether the quantum superposition of bioharmonies could occur for DAAs.

   Could quantum superposition allow to understand the observation that the increase of the parameters $K_{i(jk)}$ is accompanied by the decrease of $\epsilon_{i(jk)}$ and vice versa. Could one think that with a suitable normalization one has $\sum_{(jk)} K_{i(jk)}\epsilon_{i(jk)} = constant$. In ZEO one could regard the entire signal complex, which involves both ligand, receptor and what it induces, as a single zero energy state as a superposition of deterministic time evolutions.

   If the formation of signal complexes involves a quantum transition from a single ligand-receptor pair to a their quantum superposition involving delocalization at the cell membrane followed by state function reduction involving localiation that is selection of the complexes, the condition $\sum_{(jk)} K_{i(jk)}\epsilon_{i(jk)} = constant$ could reflect probability conservation.

4. Re-tuning of the icosahedral harmony for Z_4 and Z_2 should have a counterpart affecting the physics of AAs. Could the re-tuning be generated at the level of DAA and result from the variation of flux tube thickness as a motor action of MB? Or could it be induced by re-tuning at the level of DDNA? Tuning must be visible at the level of AAs since DX-X resonance energies must be modified.

2.2.2 Tuning and re-tuning at the level of DX-X pairing

What could the re-tuning mean for the DX-X pairing?

1. For DDNA-DNA pairing dark cyclotron photons must couple to some degrees of freedom of DNA. In the TGD framework, DNA can be magnetized [L14]. The pairing with DDNA flux tubes carrying a monopole flux with DNA strands is expected to induce magnetization along DNA due to the ring currents of electron pairs of the aromatic rings analogous to Cooper pairs.

   The simplest candidates for re-tuned frequencies are cyclotron frequencies for magnetized nucleobases. In re-tuning the cyclotron frequencies for electron pairs) assignable to aromatic rings of nucleotides would be modified in re-tuning. The change of the thickness of the monopole flux tubes defining the 12-note scale would automatically induce the re-tuning at DNA level. The re-tuning could be induced by DDNA, DRNA, and DtRNA and would not require chemistry.

2. What about the DAA-AA tuning? The only AAs with aromatic rings are Phe, tyr and trp. Could DAA-AA resonance coupling between cyclotron radiation of DAA and vibrational modes of AA with energies in the range .45-.045 eV spanning slightly more than 3 octaves?

   The general forms of the vibrational and cyclotron energy spectra are the same and for a proper value of h_{eff} the scale of the DAA spectrum is the same and resonance is possible.

   Re-tuning would require change of the conformations of the AAs so that the elastic constants would be modified. MB could induce this re-tuning as a kind of entrainment. As already proposed, this could be achieved at the level of DNA by methylation of the start codon fixing the bio-harmony.

2.2.3 Could special 3-chords act as tuning forks

Physical model for the tuning and re-tuning should be based on resonance model.

1. Tuning to a particular 3-chord or 3-chords should force the entrainment to the bio-harmony. These 3-chords would serve as an analog of a tuning fork.

   The simplest, and perhaps unrealistic, option is that the met 3-chord associated with the start codon alone fixes the bio-harmony uniquely. The met 3-chord should be different for all Z_2 harmonies.

2. The chords fixing the bio-harmony (the tables for the 3-chords of bio-harmonies are given in [L1]) should be very special and thereindeed are very special chords in the icosahedral harmonies. The epigenetic modification of the amino-acids corresponding to these 3-chords could force the re-tuning of the bio-harmony.

The triangles, whose edges do not belong to the Hamiltonian cycle, define 0-quint 3-chords containing no quint. These chords include dissonant chords possibly having semitones or tones intervals between the notes (octave equivalence and quit cycle along the Hamiltonian cycle is assumed). There are 8 different types of 0-quint chords with basic note X in 12-note scale labeled as $Xexk, k = 1, .., 8$, if the key does not matter.

1. From the Appendix one learns that there the first possess no 0-quint chords Z_4 harmony. In this case, one could argue that the bit defined by the presence or absence of the 0-quint chord defines the tuning fork, which could correspond to a methylation of some codon coding for one of the 5 AAs coded by DNA 4-plet. It is not clear, whether the choise of the codon matters.

2. By looking at the tables of 3-chords in the chord tables of the Appendix, one finds that if key matters, it is easy to distinguish between harmonies using a single 0-quint chord. If the key does not matter, it is in principle almost possible to assign different 0-quint chords to, say, met. There are 2 $Z_{2,refl}$ harmonies with 2 0-quint chords, which cannot be distinguished in this manner. If one introduces a fixed key or uses a second special 0-quint chord as a turning fork, also $Z_{2,refl}$ harmonies can be distinguished from each other.

   Interestingly, the number of BMP receptors possibly assignable to $Z_{2,refl}$ is 4 rather than 5.

3. Also tetrahedral codons define special chords in the sense that the intervals are separated by minor third. These 3-chords are identical under the octave equivalence. In the model considered in [L15], 3 of them correspond to stop codons whereas the remaining codon corresponds to trp.

2.2.4 Re-tuning as an epigenetic process

Re-tuning is an epigenetic process and can be seen as a control of MB. Methylation and its analogs are basic tools of epigenesis.

1. mRNA methylation (`https://cutt.ly/1Srm06F`) occurs after transcription and is controlled by genes coding the needed enzymes. The methylated RNA nucleobase is often called the "fifth RNA" base. Start codon AUG coding for met is methylated as also the 3-prime untranslated regions (3'-UTRs) immediately after the stop codon. This region post-transcriptionally influences gene expression.

2. The findings that the RNA of a conditioned sea snail scattered over neurons of second sea snail in Petri dish generate neuronal correlates of conditioning (`https://cutt.ly/6SuLNqk`), discussed from the TGD point of view in [L5, L7], support the view that the magnetic body of the RNA of sea snail infects the emotion/mood related to the conditioning. The emotional state, mood, of DNA and RNA would affect gene expression. Epigenesis could be based on emotional states lasting for several generations. This is natural in ZEO [L1, L7].

Hints about how the methylation could be involved with the tuning to a particular bio-harmony comes from the research of the group led by Matthias Soller [I2] (`https://cutt.ly/OSeGnJu`).

1. Post transcriptional methylation is known to occur for the few nucleotides of mRNA following the cap of mRNA, whose function has remained poorly understood. Soller and collaborators demonstrated that the two enzymes coding for the methylation of these nucleotides played an important role in the animals' reward learning process. The flies without the genes coding for the methylation showed a defect in their ability to learn the association of a specific odour with a sugar reward.

2. Earlier work by one of paper's co-authors, Prof. Rupert Fray, has demonstrated that that cap modifications are highly dynamic in mice and that these modifications played a role in transporting the mRNAs to synapses.

3. The lack of methylation implies a lack of the desired conditioning. Conditioning involves emotions, perhaps also at the molecular level: could the bio-harmony of proteins involved with the process differ from that associated with the protein activated by the odour molecules? The proteins would be out-of-tune and conditioning would not happen.

   The role of cap modifications in the mRNA transport would conform with the assumption that dark photon resonance allows the mRNA to find synapses. If the bioharmony for them is wrong there is no resonance and the transport fails.

These findings suggest the following interpretation in the TGD framework.

1. The resonance mechanism would force DDNA and DmRNA to have the same bio-harmony. The post-transcriptional methylation of the first RNA codon could re-tune and stabilize mRNA bio-harmony.

Stabilization could involve a methylation of a large enough number of special RNA codons so that it would serve as a seed of a phase transition forcing the same bio-harmony for all codons. If bio-harmonies correspond to molecular moods, this would be analogous to the spread of an emotional mood in crowd. The special codons as signatures of the mood could be especially effective inducers of this phase transition.

2. Could a 0-quint 3-chord assigned to met in the beginning of mRNA fix the Z_2 harmony almost uniquely by acting as a tuning fork. Z_4 harmony could be fixed by the absence of methylation in some mRNA nucleotide in codon coding for one of the 5 AAs [(val,pro,thr,ala,gly)] coded by 4 codons.

   Note that the methylation of 2 AUG nucleotides of met affecting the cyclotron frequencies of AUG could in principle select between the 16 bio-harmonies predicted by the simplest model. This estimate is however based on counting of bits and bio-molecules need not see each other as bit sequences as we do.

   The methylation of the mRNAs associated with several 0-quint chords could help to stabilize the Z_2 harmony at the level of DmRNA. Could the proteins obtained by splicing and involving methylation in the beginning of mRNA portions coding them consist of functional sub-units with different bio-harmony?

3. What about DNA? Could the methylation of the start codon also now help to stabilize the Z_2 bio-harmony. Only A and C DNA nucleotides of DNA strand can be methylated (as also T and G nucleotides of the conjugate strand). Note that A and G appear often in DNA repeats defining part of what was called junk DNA. One can ask whether the methylation of A and C could stabilize the bio-harmony and DNA level.

   The corresponding RNA codon contains at most one U or G nucleotide. Note that met corresponds to AUG whereas AGU corresponds to cys which together with trp (coded by tetrahedral codon) are the only sulphur containing amino-acids. Met is special in the sense that it belongs to a symmetry broken codon doublet for which ile has replaced met.

4. The first mRNA codon AUG codes for met so that the D(AUG)-Dmet pairing could induce the DAA bio-harmony and affect the vibrational frequencies of AA. This is perhaps enough for the stability of the bio-harmony. Could pretein methylation help to stabilize the bio-harmony of proteins? According to Wikipedia (`https://cutt.ly/uSiVACT`), protein methylation is a type of post-translational modification featuring the addition of methyl groups to proteins. It can occur on the nitrogen-containing side-chains of arginine and lysine but also at the amino- and carboxy-termini of a number of different proteins.

One can imagine 2 options for changing the bio-harmony at DAA-AA level. For the bureaucratic option, the re-tuning would occur at the DNA level. This would require enzymes coded by appropriate genes to re-tune the first codon of mRNA coding for AA.

For the non-bureaucratic option, DAA would re-tune AA directly by entrainment and this could involve re-methylation.

2.3 An attempt to concretize the model of ligand interactions

The following is a very naive first attempt to concretize the idea about ligand interactions as a re-tuning, whhich affects the matrices $K_{i(jk)}$ and $\epsilon_{i(jk)}$. Reader should take the following considerations as as free associations.

1. BMPs couple to 4+3 receptors. There are 3 Hamiltonian cycles with $Z_{2,rot}$ symmetry and 5 cycles with $Z_{2,refl}$ symmetry assignable to 10 amino-acids coded by 2 or single DNA (met) have 3. There are 4+3 receptors and 5+3 bioharmonies: could it be that the considered 4 receptors correspond to 4+3 Z_1 harmonies with the same Z_4 harmony and that there is also a fifth receptor of this kind but not considered?

   A priori, any protein could correspond to any bio-harmony but the correlation of DAA and bio-harmony could be forced by dynamics since the DAA-AA resonances might be possible only for certain Z_2 harmonies (and only for one of the 2 Z^4 harmonies). Suppose that the receptors indeed correspond to one particular Z_2 harmony each.

2. If the binding sites for BMP-receptor pairs correspond to single AA (in analogy with tRNA-mRNA binding), the binding site for Z_2 harmonies should correspond to a AA which is one of the 10 AAs coded by DNA doublet or singlet. The reduction of correspondence to the level of binding site AA would conform with the finding that the functional similarity of BMPs does not very closely correspond to the sequence similarity.

   In the code table there are 9 doublet AAs and 1 singlet. Symmetry breaking is present [L15]. It is not quite clear which doublets correspond to Z_2. For instance, phe could correspond to the doublet for Z_6 leaving 8 doublet AAs plus (ile,met) as a doublet with a broken Z_2 symmetry. UGG coding for trp and 3 stop codons would correspond to the tetrahedral cycle.

   By resonance condition, at most 3 receptors should correspond to more than 1 BMP as their preferred receptor.

There are also chemical constraints on the AAs acting as a binding site. Resonance condition for DAAs implies that pairing AAs are identical. The pairing AAs must be neutral and must be coded by DNA doublets or singlets. This leaves the following cases under consideration.

1. Two amino acids have amide side-chains.

   - Asparagine (Asn): $NH_2 2COCH_2$-
   - Glutamine (Gln): $NH_2 2COCH_2 2CH_2$

   These side-chains do not ionize in the normal range of pH.

2. Two side-chains contain sulfur atoms, of which one ionizes in the normal range.

   - Cysteine (Cys): $HSCH_2$-
   - Glutamine (Gln): NH_2-$COCH_2$-CH_2-

3. Three amino acids have aromatic ring structures as side-chains. Of these, tyrosine ionizes in the normal range; the other two do not.

   - Phenylalanine (Phe)
   - Tyrosine (Tyr)
   - Tryptophan (Trp)

This would give 2+2+3 =4+3 AAs. In the above mentioned option Phe is however assigned with Z_6 harmony but any other doublet AA could correspond to Z_6 harmony. This would suggest that AAs with amide side chains and containing sulphur correspond to 4 $Z_{2,rot}$ harmonies.

There are 10 BMPs with the decomposition 10=3+3+2+1+1. Using the standard biological notation, this correspondings to the decomposition [GDF5,GDF6,GDF7], [BMP5,BMP6,BMP7], —BMP2,BMP4],[BMP9], [BMP10]) to functional equivalence classes [I3]. Could the two 3:s correspond to the 3 $Z_{2,rot}$ harmonies and 2+1+1 to 4 of the 5 $Z_{2,refl}$ harmonies?

The two triplets [GDF5,GDF6,GDF7] *resp.* [BMP5,BMP6,BMP7] are weak *resp.* strong activators. Both GDFs (growth differentiation factors) and BMPs (bone morphogenetic proteins) belong to the transforming growth factor beta superfamily (TGF). If GDFs are excluded the correspondence between BMPs and receptor proteins is 1-to-1.

2.4 Could the dark matter hierarchy relate to the bio-harmony?

One can wonder how the hierarchy of algebraic extensions and algebraic evolution defining the evolutionary state for a given layer of MB affects the L-R pairings.

1. Dark 3N-photons and 3N-nucleons as dark variants of basic information molecules would correspond to Galois confined states for which the 4-momenta for components are algebraic integers summing up to ordinary integer when the momentum unit is defined by the p-adic length scale associated with the extension. Also frequencies would correspond to rational integers for Galois confined states.

2. These states depend on the algebraic extension of rationals defining $n = h_{eff}/h_0$ as its dimension although mass squared values and momenta are integer valued as also frequencies. This would give an additional context dependence. For instance, organisms at higher levels of evolution could have larger values of h_{eff} associated with the dark variants of the basic biomolecules.

3 Hen-egg problem, dark biomolecules, and resonance mechanism

The notions of magnetic body, dark matter as $h_{eff} = nh_0$ phases, dark analogs of information molecules, and resonance mechanism could allow a solution to the hen-egg problem of biology: which came first, DNA, RNA, AAs or proto-cell membrane. I have considered the hen-egg problem in [K7] and proposed a model of proto-cell in [L8].

Hen-egg problem usually means that something is missing from the conceptual picture and TGD based quantum biology suggests what this missing piece could be. The general solution of the problem in TGD would be that dark analogs of information molecules emerged first simultaneously as Galois confined states of dark proton-triplets and dark photon-triplets.

This made possible resonance communications and the basic recognition mechanism by 3-resonance for dark 3-photons. DX-X pairing was based on energy resonance and these composites were able to find each other by resonance. The reduction of h_{eff} for connecting flux tubes in their shortening liberated energy making it possible to overcome the potential wall preventing chemical reactions to occur. This is not as easy as it looks at first since metabolic energy is needed to build the valence bonds and metabolic machinery is absent in early life.

The challenge is to develop a more detailed picture around these basic ideas. I have already earlier considered several proposals for the first steps of the evolution of basic bio-molecules [K8, K9, K7] but without the recent, rather detailed, view about resonance mechanism combined with the notion of dark 3N-photon and 3N-nucleon as a dark analog of basic biomolecule [L15].

3.1 Did the DX-X pairing occur simultaneously for all basic biomolecules?

Consider first the pairing of basic information molecules X (DNA, RNA, tRNA codons and AAs). Their polymers are not considered in this section. The simplest vision is that the dark variants of basic biomolecules emerged by Pollack effect [I10, I11, I1, I13, I14] in water irradiated by solar light.

1. Pollack effect generated exclusion zones (EZs) as negatively charged regions. Part of protons were transferred to magnetic monopole flux tubes of MBs assignable to water clusters and created phases of water with a hexagonal lattice-like structure.

2. An attractive possibility is that the notion of hydrogen bonds generalizes. The monopole flux tubes could be accompanied by hydrogen bonds. This predicts a length scale hierarchy of hydrogen bonds implying long range quantum correlations in arbitrarily long scales and allowing to understand the strange thermodynamic anomalies of water. The length of the dark flux tube is proportional to h_{eff} as also the total energy consisting of Kähler magnetic and volume contribution.

3. Galois confinement as a universal bind mechanism would give rise to sequences of dark protons as bound states. The states of dark proton triplet correspond to DDNAs, DRNAs, DtRNAs and DAAs.

   The pairing of the dark analogs of biomolecules with ordinary biomolecules to form pairs DX-X gave rise to the observed basic biomolecules. DX-X pairing requires that the ordinary biomolecules have transition energies, which correspond to the cyclotron transition energies of DX for the value of h_{eff} considered. Ordinary cyclotron transitions and vibrational transitions are good candidates in this respect.

4. Energy resonance condition for the pairs gives powerful conditions and selects the allowed biomolecules. The selection has not been completely unique. In tRNA the third letter of

the chemical codon paired with one of the 32 DtRNAs need not be an ordinary nucleotide and in some viruses adenosine (A) is replaced with 2-amino-adenine ("Z") [I8] (`https://cutt.ly/hSRBS0K`).

3.2 Did proto-cell and peptides emerge first?

It is not at all clear whether the dark variants of the polymers of basic bio-molecules can emerge spontaneously. The problem is that the formation of valence bonds requires energy. This forces us to consider the TGD counterparts of the usual purely chemical proposals in which basic building bricks DNA, RNA and AAs form polymers. Now one considers an analog of polymerization at the level of DDA, DRNA, and DAA.

The findings of Montagnier et al [I6, I5, I7] discussed from the TGD view point in [L14] suggests that remote DNA replication occurs in absence of DNA template but that the presence of DNA polymerase is necessary. Dark DNA sequences generated by remote replication would appear as a template. This suggests DDNA-DNA pairing could occur by polymerization and require the presence of enzymes and metabolic energy feed.

Could proteins (Ps) have served in the role of egg in the chemical sense in the TGD framework? Could the resonance mechanism together with the TGD view about bio-catalysis make it possible to generate DP-P pairs by a polymerization-like process using DP as a template?

1. The large h_{eff} between DP and P would be shortened in a given polymerization step. Energy would be liberated as the dark flux tube bond between DP and P is shortened. This energy should make it possible to overcome the potential wall preventing the formation of the peptide bond and also provide the energy of the peptide bond, which is about .08-.16 eV and considerably smaller than metabolic energy quantum about .5 eV.

2. The thermal energy at room temperature using the definition $E_T = kT$ is .025 eV. Second definition of thermal energy is as the energy for which the distribution of black-body radiation as function of energy is maximum: this gives the energy is $E_T \simeq .12$ eV and rather near to the Josephson energy of the cell membrane for charge Z= 2e is about .1 eV.

3. The energetic requirements for AA polymerization might be satisfied by using irradiation with photon energy around thermal energy at room temperature. An interesting possibility considered in [K7] and [L8] is that a proto-cell membrane formed from lipids was present from the beginning and before the polymerization. Lipid membranes can form spontaneously and in TGD Universe they act as generalized Josephson junctions [K3, K4] and induce Josephson radiaton, which would make possible communications from cell membrane to MB. Could the Josephson radiation from the cell membrane with energy of order .1 eV provide the metabolic energy for the polymerization process of AAs?

4. In the case of DNA and RNA the carbon bond energy between two codons is about 3.2 eV and considerably larger so that the polymerization without enzymes looks highly implausible. Note also that also the formation of lipids is a problem since C-C bonds have energy 3.47 eV.

3.3 Empirical and experimental support for the model of peptide formation

There is evidence for amino acid glycine in the interstellar space (`https://cutt.ly/HSYQPmP`) but the independent confirmation is lacking. Also the formation of glycine peptides has been observed in laboratory conditions mimicking the interstellar medium (ISM).

The following summarizes the results described in the article of Serge Krasnokutski et al [I4] published in Nature. The following summarizes Krasnosutski's non-technical description of the results (`https://cutt.ly/dSYm1Sn`).

1. The ultra-low temperatures, common in astrophysical environments, have been believed to freeze out any chemistry in the dense areas of the ISM. Already the discovery of a high abundance of small organic molecules in molecular clouds was a great surprise. But also the formation of amino acids, nucleobases, lipids, and sugars in space has been confirmed.

2. What about the polymers of AAs? It has been conjectured that the condensation of carbon atoms at the surface of dust particles make possible the formation of organic molecules. Serge Krasnokutski et al indeed demonstrated the formation of glycine polymers from amino ketenes (glycine corresponds NH_2-CH_2-COOH, aminoketene to NH_2-CH-CO and polyglycine to NH-CH_2-CO) under laboratory conditions simulating the ISM conditions at temperature T=10 K (`https://cutt.ly/3SYT169`). A spontaneous(!) formation of relatively short peptides (less than 10-11 monomeric units) was found. The polymerization of amino acids under energetic processing (e.g. heat, pressure, or UV irradiation) is known to occur. Therefore, a further increase in chain length can be expected in natural environments.

   Moreover, by adding other species instead of a proton to the α-carbon atom of amino ketene (nearest to the functional group) during the polymerization, a variety of different peptide chains can be formed. Furthermore, chemical and photochemical modifications of glycine residues in peptides into other amino acid residues were also demonstrated in many works. Thus, the glycine peptides observed in our experiments can be converted into different proteins.

3. These findings fit nicely with the proposed mechanism for the formation of proteins (or at least short peptides). The mechanism is not chemical, and no radiation is needed since the generalized Josephson radiation would provide the energy of the AA-AA bond, and the formation rate does not vanish at ultralow temperatures.

3.4 How did lipids, small organic molecules, and DNA and RNA polymers emerge?

There is a temptation to say that after the emergence of proto-cell membrane and peptides, the rest was history. This is not so simple.

1. The formation of the proto-cell membrane could occur spontaneously if lipids are available. Lipids however have C-C bonds with bond energy 3.47 eV and C==C bonds with energy 6.28 eV. These energies are in the UV range.

2. Also the energies of valence bonds associated with DNA, RNA, and also other basic biomolecules are in this range. The freezing of the chemistry at ultralow temperatures does not allow the generation of these bonds since the metabolic machinery provided by ATP molecules is not present. Simple organic molecules and even amino-acids are however detected in the interstellar medium. It seems that life-as-nothing-but-chemistry dogma must be wrong.

3. The Josephson radiation associated with proto-cell membrane with an energy scale of .1 eV could help in the formation of peptides but cannot help in the more general case. Could the splitting of a hydrogen bond provide the metabolic energy quantum of .5 eV in the absence of ATP machinery? The formation of water involving O-H bonds and their dynamics at temperatures of few K do not sound plausible unless one leaves the framework of the standard chemistry.

Metabolic machinery involves a lot of control and the standardization made possible by the metabolic energy quantum. This involves a lot of control. What could have served as a controller and energy source for bond formation at ultralow temperatures of few Kelvin and in the absence of the complex metabolic machinery based on ATP. In the TGD Universe, MB carrying dark matter is the answer to the question.

1. The existence of B_{end} was originally deduced by Blackman [J1] and other researchers. They found that ELF em fields had quantum-like effects on the vertebrate brain. These effects could be understood in terms of cyclotron transitions in the "endogenous" magnetic field $B_{end} \simeq 2B_E/5$ if the value h_{eff} of Planck constant was much larger than h, $h_{eff}/h \sim 10^{13}$ was required in order to scale the energy of 10 Hz photon to that of a visible photon with frequency 10^{14} Hz.

2. The large value of h_{eff} suggests its identification as gravitational Planck constant $\hbar_{eff} = \hbar_{gr} = GMm/v_0$ given by Nottale's hypothesis [E1]. M denotes here Earth's mass and m the mass of the charged particle. This predicts that cyclotron frequencies in B_{end} correspond to dark photon energies in the visible and UV UV range. Most remarkably, the energies do not depend on the mass m of charged particles. This realizes the Equivalence Principle.

3. Visible-UV energy range is associated also with biophotons [I12, I9] discussed from TGD view point in [K5, K6]. This motivates the identification of biophotons as decay products of dark photons or possibly even dark N-photons resulting in $h_{eff} \to h$ transition. Dark photons or N-photons in this energy. Note that the Nottale hypothesis and the notion of a monopole magnetic flux tube make sense only in the TGD Universe.

4. $h_{eff}/h_0 = n$ is identifiable as a dimension of extension of rationals in number theoretic vision about TGD. n serves as a kind of IQ [L3, L4]. MB with $h_{eff} = h_{gr}$ corresponds to a rather high level of number theoretic complexity assignable to the MB of Earth as a quantum system. MB has a long scale of quantum coherence - even of the order of the scale of Earth - and is by its high "IQ" the natural "boss" and controls the dynamics of the ordinary biomatter. The molecular transitions induced by the transformations of dark cyclotron (3N-)photons would serve as a natural control tool of MB. The cyclotron condensates at MB can provicde quantized metabolic currencies in the absence of ATP machinery.

5. MB could generate already at few Kelvin temperatures various biologically important molecules by providing the metabolic energy for the formation of various valence bonds, such as carbon and peptide bonds and make possible the formation of lipids, DNA and RNA molecules and their polymers and also other basic organic molecule. Josephson radiation would in turn make possible the generation of proteins. Gravitation would be a key player in living systems and play an especially important role in the very early stage. The chemistry at ultralow temperatures would provide a direct experimental handle to the biophysics associated with MB.

3.5 What can one say about pre-tRNA

The question of what pre-tRNA could have been leads to questions about prebiotic metabolism.

1. DtRNA should have a molecular counterpart. The simplest guess is that it corresponds to an RNA type codon appearing in tRNA but somehow differing from it. Pre-tRNA could simply be the (AAC-H)3' end of the acceptor stem with AAC replaced with XYZ, where ZYZ denotes the codon part of tRNA. The addition of a hydrogen atom would relate pre-tRNA codon to ordinary RNA codon.

2. The bond energy for the pre-tRNA-AA pair as the energy of the ester bond would be about .5 eV, which corresponds to the metabolic energy quantum. Energy is therefore required to "charge" pre-tRNA. This requires metabolic energy and in the absence of ATP machinery, the energy should come from its predecessor. What prebiotic metabolism could be, will be discussed in the next section.

3. If this step works, the polymerization of tRNAs involving the transformation of the ester bond of pre-tRNA-AA to AA-AA peptide bond can occur spontaneously since the peptide bond has bond energy of order .1 eV. This would give rise to polypeptides. This process would be like a translation process for RNA but without an RNA template and therefore the outcome would be random. Also the RNA polymerization in this manner can be considered, now however the RNA-RNA valence bond has considerably higher bond energy.

4. If DRNA-RNA sequences are formed, they might be transformed to AA sequences by pre-translation process using pre-tRNA and resonance mechanism pairing DRNAs and dark counterparts of pre-tRNA-AA pairs. This would define the pre-translation process.

3.6 What could the prebiotic metabolic machinery be?

Metabolic machinery should have a prebiotic counterpart and have .5 eV as metabolic energy quantum.

1. Could the splitting of a hydrogen bond with bond energy about .5 eV provide the energy needed in the formation of pre-tRNA-AA ester bond? IR photons are most effective in causing Pollack effect in water: could also they induce pre-tRNA-AA pairing? Both options would require the presence of water. In principle, the proposed mechanism could lead to a generation of water molecules (the energy of O-H bond is 4.81 eV) already at temperatures of few Kelvin.

2. Could MB somehow provide the metabolic energy quantum? Gravitational flux tubes are in a central role in the TGD inspired quantum biology. In [L13] it was observed that the gravitational binding energy of a nucleon in the gravitational field of Earth is .67 eV. This is somewhat larger than the metabolic energy quantum. A dark proton at a distance of about $.34R_E$, R_E Earth radius, from the surface of Earth has gravitational binding energy of .5 eV.

   The bond energy of the hydrogen bond is .5 eV. Could it correspond to the reduction of the gravitational binding energy due to the delocalization of a dark proton to a gravitational flux tube? Could the hydrogen bond become dark with $h_{eff} = h_{gr}$. The transformation of a dark proton at the gravitational flux tube of MB to an ordinary proton implies a localization having interpretation as falling to the surface of Earth. Could this provide the metabolic energy quantum?

3. Since the metabolic machinery should have developed from its pre-biotic counterpart, also ADP $\rightarrow$ ATP transition should involve the transformation of dark nucleon to ordinary one as a basic process occurring in the scale of Earth!

4. For electrons the gravitational binding energy at height $.34R_E$ is about .25 meV. This corresponds to the energy of photons in the microwave background. Could this define a second metabolic energy quantum important in scales by a factor $m_p/m_e \sim 2^{11}$ longer than nanoscale about 1 nm assignable to DNA. This is the length scale of the cell nucleus, microtubules and axons. Intriguingly, the minimal fluctuations of membrane potentials correspond to the so-called miniature end plate potentials .4 mV (`https://cutt.ly/HSJIn76`).

This proposal looks nice but challenges the assumption that basic biomolecules are always paired with their dark counterparts. Consider DNA double strand.

Dark codon corresponds to three dark nucleons so that the total gravitational binding energy would be 1.5 eV. For paired codons of the double DNA strand the gravitational binding energy would be about 3 eV. The total number of hydrogen bonds per base pair is 2 or 3 giving energy of 1-1.5 eV per base pair and bond energy of 3-4.5 eV per codon. This is not far from the estimate of 3 eV for the gravitational binding energy of a *single* dark codon, not two! Could this mean that there is only a single dark DNA strand and the formation of hydrogen bonds between DNA strands corresponds to the formation of dark DNA? If so, single DNA and RNA strand, and AA would have no hydrogen bonds. Do they have any dark counterparts? A natural mechanism allowing darkness of also single stranded bio-molecules would be the formation of hydrogen bonds between surrounding water molecules and strand implying the delocalization of dark protons at flux tubes. This is known to occur for all polar biomolecules. This would require metabolic energy feed. If this is the case the formation of hydrogen bonds between base pairs reduces the metabolic energy costs and could also compensate for the loss of DNA-water hydrogen bonds due to the reduction of the area between DNA strand and water when a double DNA strand is formed.

$$\begin{array}{llll} CEG \equiv C\ , & CD\sharp G \equiv Cm\ , & CD\sharp F\sharp \equiv C^o\ , & CEG\sharp \equiv Caug\ , \\ CFG \equiv C4\ , & CF\sharp G \equiv C4_+\ , & CGG\sharp \equiv C6_-\ , & CGA \equiv C6\ , \\ CGB\flat \equiv C7\ , & CGB \equiv Cmaj7\ , & CGC\sharp \equiv C9_-\ , & CGD \equiv C9\ . \end{array} \tag{4.1}$$

Table 1: Notation of chords inspired by popular music notations.

4 Appendix: Tables of basic types of 3-chords for icosahedral harmonies

4.1 Icosahedral harmonies as Hamiltonian cycles

One can find the list of Hamiltonian cycles at `http://tinyurl.com/yacgzm9x`. The edge $\{1, 2\}$ is fixed and cycles are oriented so that there are 1024 of them. All of them are relevant from the point of music interpretation and the change of orientation corresponds to major-minor duality, albeit not in the simplest sense. Note that this duality does not affect the characteristics listed above.

The general following general results hold true as one can learn at `http://tinyurl.com/pmghcwd`. One can classify the cycles using their symmetries which can correspond to isometries of icosahedron leaving them fixed or to a reflection taking the vertex n at the cycle to vertex $12 - n$. This symmetry is not same as change of orientation which is purely internal operation and cannot change the cycle.

One can even find images of the cycles possessing symmetries at `http://tinyurl.com/y8ek7ak8` and deduce the triplets n and p characterizing them by visual inspection. Also one can write explicitly the 3-chords defined by the three kinds of faces. I have deduced the triplets n and the 3-chords defining the harmony by the inspection of the images. "Bio-harmony" (4, 8, 8) forced by the model of extended genetic code involving also the 21st and 22nd amino-acids is of special interest.The classes of cycles with symmetries 6-fold rotational symmetry and two distinct reflection symmetries realize it.

Before continuing some terminology and notation is in order. Take C as the major key. Submediant or relative minor corresponds to Am, subdominant (sharp or flat) to F major (F) or Fminor (Fm), dominant to G. The notation for chords is such that quints correspond to subsequent notes in the chord. For 1-quint chords this means that first two notes define the quint.

Table 1 summarizes the notation inspired by the popular music notation. The basic difference is that the third is in most cases excluded so that the emotional character of the chord is not fixed. Besides these notions it is convenient to introduce additional notations for various dissonant chords appearing as 0-quint chords.

$$\begin{array}{llll} CC\sharp D \equiv Cex1\ , & CC\sharp D\sharp \equiv Cex2\ , & CDD\sharp \equiv Cex3\ , & CDE \equiv Cex4\ , \\ CD\sharp E \equiv Cex5\ , & CC\sharp E \equiv Cex6\ , & CDF\sharp \equiv Cex7\ , & CDG\sharp \equiv Cex8\ . \end{array} \tag{4.2}$$

Clearly, the sets {ex1}, {ex2, ex3}, {ex4, ex5, ex6}, {ex7}, {ex8}, corresponds to the span of 2, 3, 4, 6, 8 half notes for the chord.

The following summarizes the results. Note that $Cex7$ can be seen as part of $D7$ chord.

1. There are 6 collections of cycles without any symmetries containing 48 cycles each: these 48 cycle are mutually isometric so that one can say that there 6 different harmonies.

2. There is a collection with 6-fold rotational symmetry, 48/6=8 examples. $n = (2, 12, 6)$. The chords of this scale define 6-note scale involving only total steps. CDF and its 6 translates by integer number of steps define 6 1-quint chords. $CE\flat G$ (Cm) and its 6 translates (they obviously correspond to the 6-fold rotational symmetry) define also 6 1-quint chords. The reflection transforms these series to those defined by $GB\flat G$ and its translate and byFAC (F major) and its translates. Impressionists like Debussy used 6-note scale of this kind.

Half-octave shift is an exact symmetry. 1-chords lack the third so that one cannot assign to 3-chords any emotional quality. The extension to 4-chord can however bring either "happy" or "sad" quality. Clearly, these harmonies have "jazzy" character.

0-quint chords are $Faug \equiv FAC\sharp$ and $Gaug \equiv GHD\sharp$ are transformed to each other by both half-octave shift and inversion.

3. There are 2 collections with 2 distinct reflectional symmetries with 12=48/4 representatives in each. Half-octave scaling is a symmetry of both these scales as one might guess.

   The first cycle (see **Fig. ??**) has $n = (0, 16, 4)$ so that there are no 0-quint chords which in general are dissonant. Second cycle (see **Fig. ??**) realizes $n = (4, 8, 8)$ bio-harmony and deserves some comments. It will be discussed in detail later.

   (a) The 8 2-quint chords consist of $B\flat FG \equiv B\flat 9$, C9, F9, G9 and their half-octave scalings. Clearly, the simple four-note scale appears here.

   (b) Using the popular notion introduced earlier, 1-quint chords consist of two 4-plets $Dmaj7$, $E9_-$, $A7$, $A6$ and $G\sharp maj7$, $B\flat 9_-$, $D\sharp 7$, $D\sharp 6$ related by half-octave shift. The harmony contains no "simple" major or minor chord and only the extension to tetrahedral harmony can provide them. The same is true for the second bio-harmony.

   (c) The 4 0-quint chords are $Cex3 \equiv CDD\sharp$ and $Eex2 \equiv EFG$ and their half-octave scalings $F\sharp ex3 \equiv F\sharp G\sharp A$ and $B\flat ex2 \equiv B\flat BC\sharp G$.

4. There are 3 collections with Z_2 rotational symmetry with $48/2 = 24$ representatives in each. The triplets n are $(0, 16, 4)$ (see **Fig. ??**), $(2, 12, 6)$ (see **Fig. ??**), and $(4, 8, 8)$ (see **Fig. ??**).

   All these harmonies are symmetric with respect to half-octave shift (tritonus), which obviously corresponds to the Z_2 rotation. Tritonus would not have been tolerated by catholic church! This symmetry characterizes all 3 harmonies. Basic 3-chords do not contain pure minor and major chords. The reflection of the scale does not leave the collection of chords invariant but it is not clear whether this corresponds only to a change of scale, probably not.

   Consider the (4, 8, 8) case (see **Fig. ??**).

   (a) The 8 2-quint chords appear as four-plet $H9, C\sharp 9, D\sharp 9, F9$ and its half octave shift (tritonus interval) acting as a symmetry of the harmony. 2-quint chords are always of type X^9 (note that the third is missing) but also 1-quint chord can be of form X^9 as explicit construction of chords demonstrates: I have denoted these 1-quint chords by symbol $X4$ (CDG is obviously equivalent with CDG).

   (b) Using the popular music notation introduced earlier, the 8 1-quint chords are $D7, Amaj7, A4_+, E7$ and their half-octave shifts $G\sharp 7$, $D\sharp 7, D\sharp 4_+, B\flat 7$.

   No major and minor chords are included and only the extension to tetra-icosahedral harmony can provide them and also break the symmetry giving rise to well-defined key.

5. The four 0-quint chords appear in two types. $D\sharp ex2 \equiv D\sharp EF\sharp$ and its half-octave shift $Aex2 \equiv AB\flat C$ plus $Hex3 \equiv HC\sharp G$ and its half-octave shift $Fex3 \equiv FGC\sharp$. According to usual thinking these chords involve dissonances. This dissonance character is a rather general phenomenon for the harmonic loners and classical views about harmony would exclude them as asocial cases! In the case of maximally symmetric harmony the loners are diminished chords and thus not so dissonant. In some cases there are no 0-quint chords.

There are 5 collections of 20 chords with Z_2 reflection symmetry (see **Figs. ??**, **??**, **??**, **??**, **??**). The integer triplets n are $(2, 12, 6), (2, 12, 6), (4, 10, 6), (2, 12, 6), (2, 12, 6)$. Bio-harmony has a representative also in this class (see **Fig. ??**). The half-octave scaling symmetry is broken for these harmonies.

Some comments $(4, 8, 8)$ case are in order (see **Fig. ??**).

1. 2-quint chords appear as reflection related multiplets $C9, D9, H\sharp 9, D\sharp 9$ and $C\sharp 9, H9, F9, B\flat 9$.

$(\mathbf{n_0}, \mathbf{n_1}, \mathbf{n_2})$	**0-chords**	**1-chords**	**2-chords**
(2, 12, 6)	$(Faug, Gaug)$	$(Cm, Dm, Em, F\sharp m, G\sharp m, B\flat m)$,	$(C9, D9, E9, F\sharp 9, G\sharp 9, B\flat 9)$.
		$(F6, G6, A6, B6, C\sharp 6, D\sharp 6)$.	

Table 2: Table gives various types of 3-chords for harmonies with Z_6 rotational symmetry. Note that half-octave shift is an exat symmetry. Note that $G^{aug} = CEG\sharp, F^{aug}$ act as bridges between the groups related by half octave shift. The chords have been arranged so that they form orbits of Z_6. "Amino-acid chords" correspond to preferred chords at the orbits.

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$(\mathbf{n_0}, \mathbf{n_1}, \mathbf{n_2})$	**0-chords**	**1-chords**	**2-chords**
(0, 16, 4)		$(D7, D6, G\sharp 7, G\sharp 6)$,	$(B\flat 9, B9, E9, F9)$.
		$(G4+, A9-, C\sharp 4+, D\sharp 9-)$,	
		$(Emaj7, Gmaj7, B\flat maj7, C\sharp maj7)$,	
		$(C9-, A9-, F\sharp 9-, D\sharp 9-)$.	
(4, 8, 8)	$(Cex3, Eex2, F\sharp ex3, B\flat ex2)$.	$(Dmaj7, E9-, A7, A6)$,	$(B\flat 9, F9, C9, G9)$.
		$(G\sharp maj7, B\flat 9-, D\sharp 7, D\sharp 6)$.	$(E9, B9, F\sharp 9, C\sharp 9)$.

Table 3: Table gives various types of 3-chords for the two harmonies with $Z_4 = Z_2^{rot} \times Z_2^{refl}$ symmetry. 4-plets represent the orbits. First cycle has no harmonic loners. Second cycle gives rise to bio-harmony (4, 8, 8) for which 0-quint chords are dissonant. Both cycles have Z_2 rotation symmetry acting as a vertical reflection symmetry in figures and realized also as half-octave shift so that 4-plets contains chords and their half-octave shifts. The genuine reflection symmetry acts as a horizontal reflection symmetry in figures. The cycles correspond to figures **??**, **??**

2. 1-quint chords appear as symmetry related mutiplets $G, D7, Amaj7, E7$ and $C\sharp m, F\sharp 6, H6_-, E6$. Key G major and $C\sharp$ minor would be natural looking keys even without tetrahedral extension. For the mirror image $B\flat$ minor and E major would be the natural looking keys. For extension E major would be the key.

To sum up, half octave shift is a symmetry of all harmonies expected those having only Z_2 reflection symmetry, and fails thus also for the corresponding bio-harmonies. The tables below give list for the three types of 3-chords for the 11 harmonies possessing symmetries. A 3-chord with n quints is called n-quint chord. The harmonies are labelled by integer triplets (n_0, n_1, n_2), n_i gives the number of n-quint chords.

The reversal of the orientation for the cycle induces the transformation $C \leftrightarrow C$, $F\sharp \leftrightarrow F\sharp$, $H \leftrightarrow C\sharp$, $F \leftrightarrow G$, $D \leftrightarrow B\flat$, $E \leftrightarrow G\sharp$, $A \leftrightarrow D\sharp$ and produces a new scale with minor type chords mapped to major type chords and vice versa.

The standard notation of chords used in popular music is used. One must however remember that all 3-chords except those which are simple majors or minors lack the third so that their emotional tone remains uncharacterized. For instance, $C6$ does could be replaced with $Cm6$ and $G7$ with $Gm7$. The reader can check the chords by direct inspection of the figures. The convention used is that vertex number 1 in Hamiltonian cycle corresponds to C note.

4.2 Tables for the 3-chords of icosahedral harmonies

The following tables give the 3-chords of the icosahedral harmonies.

4.3 Illustrations of icosahedral Hamiltonian cycles with symmetries

The figures below illustrate the Hamiltonian cycles involved. Quite generally, the Z_n symmetry acts by a shift by $12/n$ quints along the cycle and the orbits of chords consist of at most n chords of same type as the reader is encouraged to verify.

$(\mathbf{n_0}, \mathbf{n_1}, \mathbf{n_2})$	**0-chords**	**1-chords**	**2-chords**
(0, 16, 4)		$(Em, B\flat m), (Cm, F\sharp m),$	$(D9, G\sharp 9),$
		$(G6, C\sharp 6), (A6, D\sharp 6),$	$(E9, B\flat 9).$
		$(D4+, G\sharp 4+), (B4+, F4+),$	
		$(Cmaj7, F\sharp maj7), (G6-, C\sharp 6-).$	
(2, 12, 6)	$(Aex4, D\sharp ex2).$	$(Am, D\sharp m), (G9-, C\sharp 9-),$	$(C9, F\sharp 9),$
		$(C4, F\sharp 4), (E4+, B\flat 4+),$	$(A9, D\sharp 9),$
		$(Dmaj7, G\sharp maj7),$	$(D9, G\sharp 9).$
		$(Bmaj7, Fmaj7).$	
(4, 8, 8)	$(Aex2, Hex8, D\sharp ex2, Fex8).$	$(D7, G\sharp 7), (Amaj7, D\sharp maj7),$	$(G9, C\sharp 9), (A9, D\sharp 9),$
		$(A4+, D\sharp 4+), (E7, B\flat 7).$	$(B9, F9), (E9, B\flat 9).$

Table 4: Table gives various types of 3-chords for harmonies with Z_2 rotation symmetry acting as half-octave shift. The doublets represent 2-chord orbits. The cycles correspond to figures **??**, **??**, and **??**.

$(\mathbf{n_0}, \mathbf{n_1}, \mathbf{n_2})$	**0-chords**	**1-chords**	**2-chords**
(2, 12, 6)	$(F\sharp ex3, Hex4),$	$(Am, D\sharp), (A6, D\sharp 7),$	$(C9, F9), (B9, F\sharp 9),$
		$(D7, B\flat 6), (G6-, Fmaj7),$	$(E9, C\sharp 9).$
		$(D4+, B\flat 9-), (E9-, G\sharp 4+),$	
(2, 12, 6)	$(Dex4, Hex4).$	$(F, Fm), (C6-, B\flat maj7),$	$(C9, D\sharp 9),$
		$(D7, G\sharp 6), (Gmaj7, D\sharp 6-).$	$(D\sharp 9, C\sharp 9),$
		$(C\sharp 4-, A4+), (E4+, F\sharp 6).$	$(E9, B9).$
(4, 8, 8)	$(Fex1, D\sharp ex3, G\sharp ex1, Aex2).$	$(E7, E6), (Amaj7, B9-),$	$(D9, B9), (C9, C\sharp 9),$
		$(G, C\sharp m), (D7, F\sharp 6).$	$(F9, G\sharp 9), (D\sharp 9, B\flat 9).$
(2, 12, 6)	$(Hex3, Eex7).$	$(D7, G\sharp 6), (G, D\sharp m),$	$(C9, D\sharp 9),$
		$(F, Fm), (C6-, B\flat maj7),$	$(D9, C\sharp 9),$
		$(A9-, C\sharp 4+), (E7, F\sharp 6).$	$(E9, B9).$
(2, 12, 6)	$(F\sharp ex2, Fex3).$	$(F, B\flat m), (C7, G\sharp 6),$	$(B\flat 9, D\sharp 9),$
		$(Amaj7, B9-), (E6, E7),$	$(C9, C\sharp 9),$
		$(G, C\sharp m), (D7, B6).$	$(D9, H9).$

Table 5: Table gives various types of 3-chords for harmonies with single reflection symmetry. The cycles correspond to figures **??**, **??**, **??**, **??**, **??**.

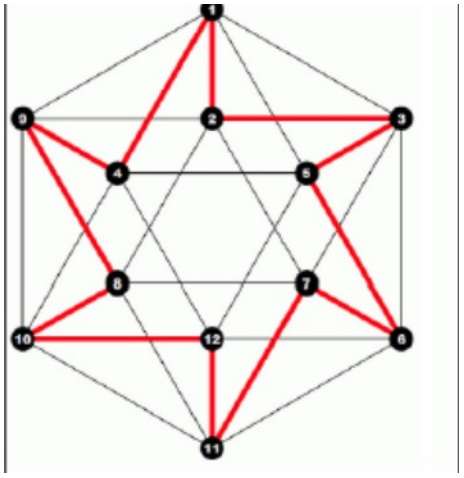

Figure 1: $(n_0, n_1, n_2) = (2, 12, 6)$ Hamiltonian cycle with 6-fold rotation symmetry acting shifts generated by a shift of 2 quints.

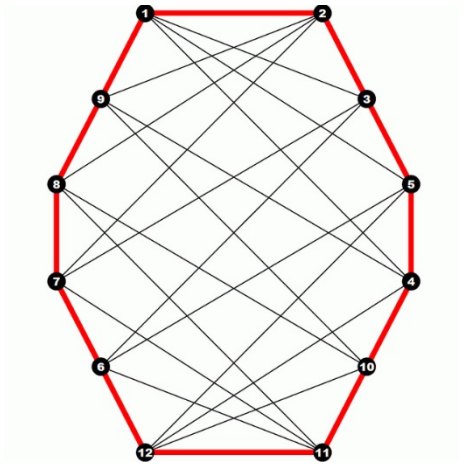

Figure 2: $(n_0, n_1, n_2) = (0, 16, 4)$ Hamiltonian cycle with 4 reflection symmetries generated by reflections in vertical and horizontal directions.

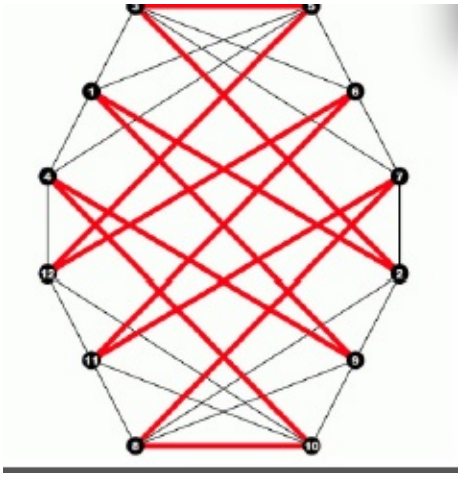

Figure 3: $(n_0, n_1, n_2) = (4, 8, 8)$ Hamiltonian cycle with 4 reflection symmetries.

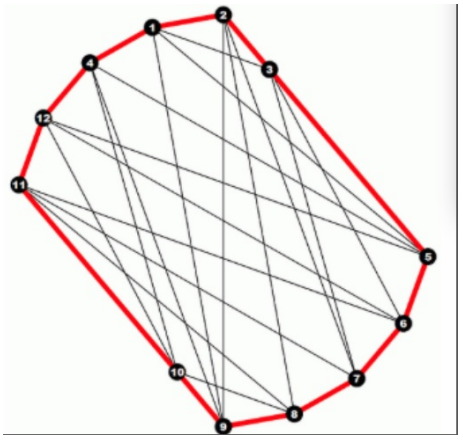

Figure 4: $(n_0, n_1, n_2) = (0, 16, 4)$ Hamiltonian cycle with 2-fold rotational symmetry realized as 6-quint shift along the cycle.

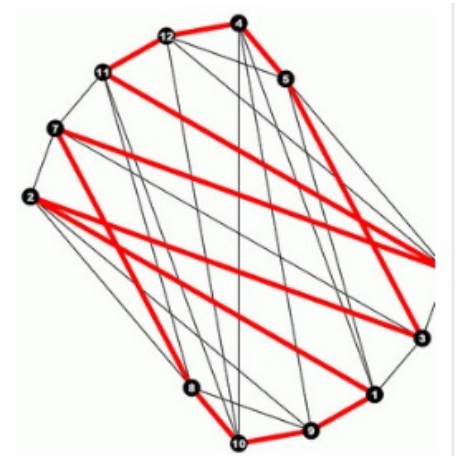

Figure 5: $(n_0, n_1, n_2) = (2, 12, 6)$ Hamiltonian cycle with 2-fold rotation symmetry.

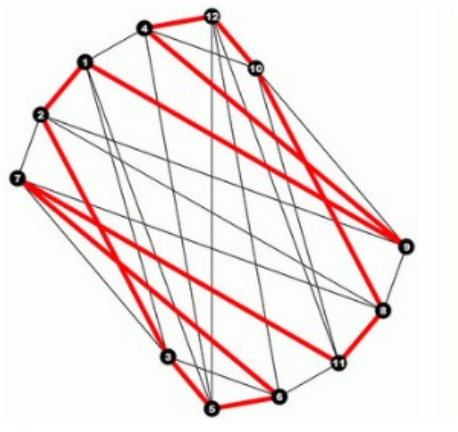

Figure 6: $(n_0, n_1, n_2) = (4, 8, 8)$ Hamiltonian cycle with 2-fold rotation symmetry.

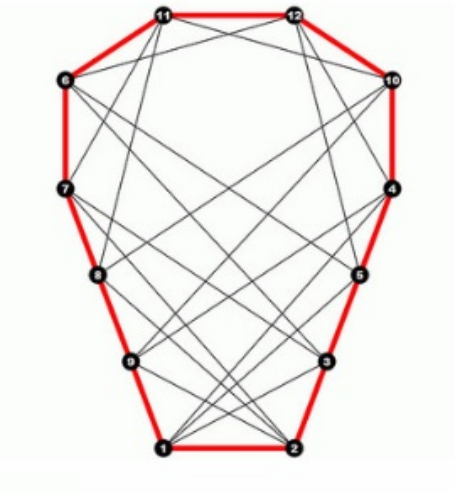

Figure 7: $(n_0, n_1, n_2) = (2, 12, 6)$ Hamiltonian cycle with 2-fold reflection symmetry realized as horizontal reflection

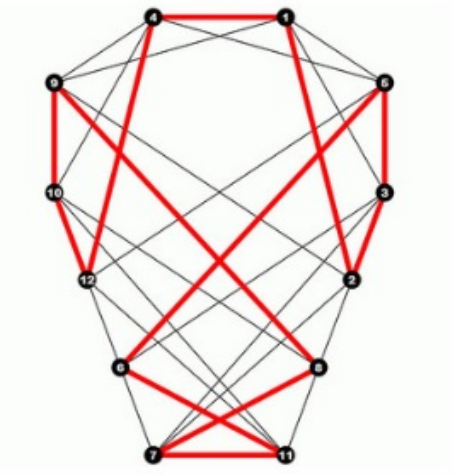

Figure 8: $(n_0, n_1, n_2) = (2, 12, 6)$ Hamiltonian cycle with 2-fold reflection symmetry.

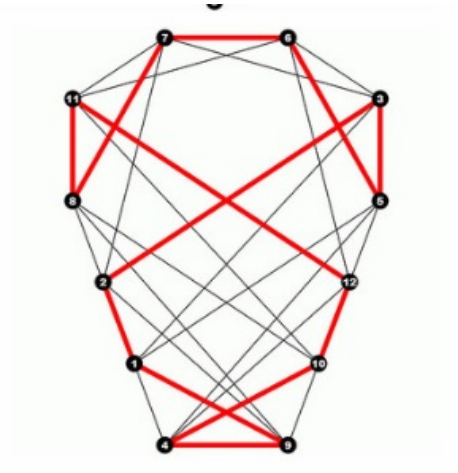

Figure 9: $(n_0, n_1, n_2) = (4, 8, 8)$ Hamiltonian cycle with 2-fold reflection symmetry.

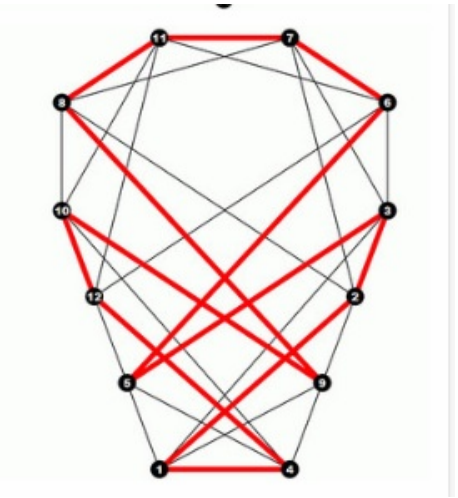

Figure 10: $(n_0, n_1, n_2) = (2, 12, 6)$ Hamiltonian cycle with 2-fold reflection symmetry.

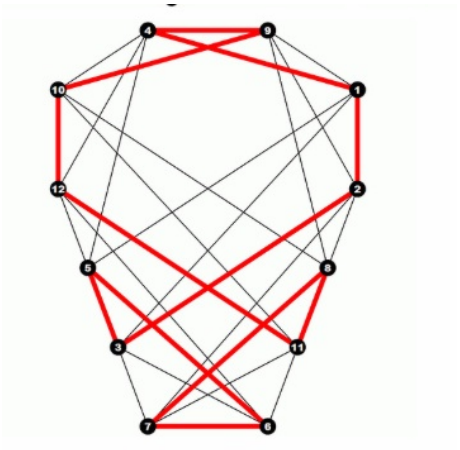

Figure 11: $(n_0, n_1, n_2) = (2, 12, 6)$ Hamiltonian cycle with 2-fold reflection symmetry.

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