Cancer as a script and possible implications on workings of genome

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Abstract

There is a need for an genomic theoretical framework which would allow for phenomena observed in cell and also explain evolution of cellular life. The search for a genomic explanation to cancer lead to the concept of the genomic script which extends its influence over the workings of genome of a normal cell too. This framework explains multiple phenomenon like the development of an embryo, differentiation of cells, and genomic workings of cancer. It also explains the evolution of unicellular and multicellular organisms. Yet it remains a simple construct; a perennial loop with adaptor loops constituting the genomic script.

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Introduction

There is an urgent necessity for a genomic theoretical framework in biology. The more we discover about the genome the more discreet identities are identified (1–4). Though the studies are immaculately planned and executed, the results are difficult to explain in context of a bigger picture (5,6). This makes it even harder when conclusions of a new study deconstruct the theoretical structure build by the preceding studies (7–9). The completion of the human genome project has only increased our woes. There is no common theory that explains the massive genomic machinery which keeps surprising us at every turn. The state of affairs for the complex disease of cancer is the same. The number identified cancer genes keep rising (4,10,11). There seems to be no “AHA It's you then” moment with any of the discovered cancer genes. Many other factors have been implicated in cancer increasing the complexity even more (12,13). Nevertheless there are those who expect a few underlying principles forming the basis of cancer (14–17). They expect a common theme in cancer.

A study reported two sets of genes which are highly expressed in neoplastic progression and undifferentiation (18). Functional networks of these genes show a characteristic pattern which indicates that the progression of cancer could be due to a change in gene networks (Figure 1 and 2). But another explanation would be that the change observed was the outward manifestation of a change occurring in an underlying process. Simply put an alteration in this underlying process is reason why the gene networks have changed. That underlying process is the genomic script. Functional networks can be generated using STRING (19). Just pop the list of the genes in the web server. You can adjust the required confidence score and number of interactors shown to your liking. Avoid low confidence score or high number of interactors otherwise the resulting functional network will contain too many interactions. Other than that your are good to go. The neoplastic signature clearly shows

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sub-networks and the undifferentiated network shows a cohesive central network. This result is consistent even if you keep changing the values.

In this writing I present a framework of genomic script. I use this framework to explain cancer progression. I extend this to explain certain aspects of cells like life in extreme habitats, antibiotic resistance and development of precision of function in cells of our body. But let me discuss the functional networks of cancer metasignature genes first. This would help us in grasping the concept of genomic script.

Cancer as a script

The metasignature genes are randomly located on the chromosomes and are not biased or limited to a specific chromosome indicating that the whole genome is accessed for expressing genes required for cancer generation and progression (20).These genes are expressed in most of the normal tissues and are essential for various cellular processes which are important for survival of even normal cells (21). The central network of undifferentiated metasignature dominates the network generated by combining the two lists of genes which distinctly shows the genomic tendency to favour the progression of cancer (Figure 3). Probably a script for cancer generation and progression does exist. The execution of this script causes the progression of a normal cell to a cancerous one.

What is a genomic script?

A *Genomic script* is a sequence of accessing genome which loops onto itself. It could be made of sub-loops. The result of an executed script is a sustained effect that we can observe in the cell. The standard model is that in a cell a genomic script consists of a central loop or the perennial loop and from it arise the side loops or the adaptor loops. The side loops can have time-hurried (positive feedback loop) or time-delayed (negative feedback loop) effect on the central loop. It will become clear as we proceed with the present discussion that

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cancer is a type of genomic script and that genomic scripts may have a bigger role to play in the life of a cell.

Explaining functional networks using genomic script

The sub-networks in the neoplastic functional network are similar to the smallest gear which rotates the fastest (Figure 1). These sub networks or the side loops are executed more than the central loop which may be due to the time delayed effect of sub networks on the central loop (Figure 4). Hence they are observed prominently while the "large gear" or central loop is not. If sub-networks weaken or collapse into the central loop then the central loop would rotate faster since it is free of the time-delayed effect of the side loops. This might be the reason why a central network is prominent in undifferentiated and the combine functional network (Figure 5). The side loops consists of those genes which help in maintenance of the cell while the central loop is mostly cell proliferation related genes and as cancer cells proliferate they fail to build up cell differentiation associated characteristics which are usually observed in normal tissue cells resulting in their "undifferentiated" appearance. The tendency of the central loop is to go faster and tendency of the side loops is to delay it. In cancer weakening of side loops sends the central loop into a frenzy yielding non-stop divisions. But why have the side loops collapsed?

Role of gene networks in a genomic script

Progression of a cell from a healthy to an undifferentiated cell is characterised by changes in gene network. These changes are just snapshots of a highly dynamic genomic script framework which ladders within the genome. In this framework, the gene network is modified avoiding any collapse. The genes, which are the constituents of the network, are moved or replaced till a new configuration is achieved. This is the shifting of genomic script. Gene networks act like tent pegs to the genomic script. Rearrangement of these "pegs" is

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essential to achieve a new route. Execution of script establishes gene networks and in turn gene networks peg down the script. This interaction provides flexibility and robustness to the process. Individual genes could be targeted but the network could easily survive by rerouting its internal connections leaving the script unaffected. The best treatment strategy for cancer would be to trigger the cell to generate strong side loops and the rest would be done automatically.

Genes and the genomic script

Varying expression of specific genes within a network could affect its overall outcome. This change could be critical to the execution of the script since gene networks act as its pegs. In this way the genes within a network indirectly but effectively impact the script. The concept of genomic script enables us to think of oncogenes and tumor-suppressor genes as potential locks on the cancer script. The varying expression of these genes could trigger or prohibit its execution. A study reports that varying expression of specific genes can trigger a change in the state of a select cancer cells *i.e.* from benign to malignant (22). In my opinion the switching of states is actually caused by a shift in the genomic script. On the other hand the script influences the function of the genes recruited in the network. A recent study reports that certain cancer genes exhibit duality in their function under different experimental settings strengthening the idea that the function of a gene is heavily influenced by the genomic context in which it is expressed (9,23). This is further supported by findings of another study where researchers have reported certain disease related gene orthologs in plant, yeast and worm (24,25). These studies show that execution of the script takes precedence over the function of an individual gene. All such candidate genes are important for conducting further studies since they expose the subtle relationship between genes and the script.

The framework of genomic script plays an extended role in a normal cell too. I discuss

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this role of the framework in different scenarios and as we continue I hope a distinct picture of its importance would emerge.

Observing genomic script

The case of developing embryo

An embryo of a vertebrate species exhibits different morphological features during the various stages of its development. These are similar to embryonic stages of other closely related species. Experts have expressed varying opinions regarding this phenomenon but generally agree that there is some kind of evolutionary significance to it (26–28). I find a developing embryo to be a fascinating example for observing scripts in action. It could be assumed that cells of an embryo are passing through different stages of genomic script which belong to evolutionarily earlier but closely related species till it reaches its native script. The primitive versions of the script are locked in. At every step in evolution a distinct version of genomic script would have been deployed and tight controls would have been put in place so that only the right native script remains active. But in the case of cancer this lock down is overcome. In a cancer cell, the collapse of the side loops probably opens the lock initiating the script that causes cancer. The tendency to survive and the no coordination policy with the surrounding tissue indicates that cancer is not the native script of the organism. So when the DNA is loosened it may be falling back to a primitive script.

The case of cell differentiation

Quiescence and senescence are terms describing states of growth arrest of a cell. While senescence is permanent quiescence is temporary but there are no hard boundaries for these states (29,30). Growth arrest is coupled with process of cellular differentiation which is a process where a stem cell becomes a specialised cell capable of performing a specific function (31). The proliferation capabilities of a cell diminish as it progresses towards

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differentiation. In human body, cells of different tissues show different levels of growth arrest allowing them replenish the specialised cell population of that tissue accordingly. Growth arrest of a cell has been implicated in major complex biological processes like tumor suppression or promotion, tissue repair and aging (30,31). Genomic script framework easily accommodates these states (Figure 6). A well differentiated cell has a specific pattern of strong side loops since they effect the function of the cell. Side loops push the cell towards differentiation. With each consecutive division, the side loops grow stronger acting as brakes to the cell division cycle by influencing the central loop to grind to a halt (Figure 6). After a limited number of divisions the cell enters the growth arrest phase. A specific pattern of side loops is achieved for each cell type and this pattern is refined achieving the precision in function of that cell. One of the many examples of precision in function is acid production by gastric parietal cells. The produced acid has a consistent pH of 1.5 to 3.5 (32). I'm sure other examples such as the functioning of cardiac pacemaker cells and muscle cells of the heart (33) and neurons and glia of the nervous system (34) will come to the reader's mind.

The case of cancer like native script

Since cancer seems to be an alternative script that is executed there is a possibility that a script similar to cancer could exist as a native script in other organisms. This script would be beneficial to the organism enabling it to survive. By looking at general morphology of tumors, which ranges from being shapeless to exhibiting basic symmetry, and the tendency of a cancer cell to lose all the trademarks of differentiation, we can look for similar scripts in organisms which evolved before there was a definitive symmetry for example sponges of the phylum Porifera. These organisms are potential candidates since they lack definitive body symmetry and exhibit primitive tissues with no organ developement. An interesting point to note is that at the base of the kingdom metazoa or animalia lay the branching of Parazoa and Eumetazoa.

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While the eumetazoans evolved into all the animals we know today, the parazoans which remain near to the branching point are represented by a single extant phylum porifera (35,36). Could it be that genome of cancer cells has fallen back to a script similar to the organisms of that period in evolution? If it is so then poriferans are ideal organisms to focus our studies on. The undifferentiated cancer cells show no distinguishable appearance which could mean that the cell's DNA has been freed further enabling the script to fallback to a script similar to organisms placed still lower in tree of life. If the similar script is found it would be beneficial in studying the genomic characteristics of cancer script.

Evolution and the genomic script

Enabling unicellular life

Evolution is the copyright of prokaryotes. They are the pioneers who terra-formed this planet. My discussion here deals with prokaryotes. Eukaryotes have it easy in comparison to hazards faced by their predecessors. Every organism is adamant in holding on to its genomic state even if conditions are otherwise. Maintenance of this state enables cellular life to survive and propagate. Consider an extremophile like *Thermococcus gammatolerans*, in order to survive it had to develop the inherent resistance to radiation (37). Even the rare and precise mutations do not confer this organism with the ability necessary to survive in such harsh environment. The organism does survive on its own by responding aptly to the mutation that it's DNA had received or to any other environmental stimuli. It is here the genomic script comes into play providing a solid framework based on which the cell could respond in such a situation. If nescessary the script would be shifted to balance any change in environment. The whole concert of moving gene-networks and rerouting script would be undertaken till the final desired effect is achieved. During the shift many routes would have been tried and many genes might have been dropped or recruited in gene networks. But once the required route

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that which confers radiation resistance to the cell is achieved it gets fixed allowing *T. gammatolerans* to consistently resist high radiation.

Scripts in extreme and normal habitats

Singled celled organisms interact with the environment directly allowing their genomic scripts to shift routes to meet the demand. The two microbial domains of the accepted system of the three domains of life get fuzzier when the framework of genomic scripts is applied to them. For example when the majority of extremophiles are Archaea but the Bacterial species are not far behind. If one can quote an archaean *T. gammatolerans* for radiation resistance another can quote a bacterium *D. radiodurans (37,38)*. It's the same when one quotes examples for mesophiles. Bacterial species dominate but one can state many mesophilic archaeal species which are being studied currently (39). So here I apply genomic script for differentiating between the organisms. Do bear in mind that any of the following types could a Bacterium or an Archaean. There is a broad difference between scripts of a mesophile and an extremophile. The genomic script diverged into two broad possibilities. The script of extremophiles is a specialist script which has sacrificed its flexibility. This script evolved to perfection due to constant exposure to extreme but stable conditions of the environments like early earth biospheres and the hydrothermal vents. It holds up precisely to the demands of extreme habitats as described earlier in the case of *T. gammatolerans*. These organisms do not allow the script to fluctuate once the right route is achieved. So even a minor change in the environmental variables could kill the organism instantly. During evolution, genomes of extremophiles would have developed some kind of DNA binders or lockers which would help them maintain script rigidity.

If we leave the extreme habitats, normal habitats are occupied by unicellular organisms with flexible scripts which enable them to tackle the changing conditions. It has to

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be borne in mind that the environmental variables of a normal habitat fluctuates within ranges which allow survival of high order eukaryotes. In another perspective it means that these stable conditions are the ranges that biosphere of planet earth settled in which turned out to be supporting the evolution of mesophilic multicellular organisms. In such a habitat the environmental stimuli appear and disappear intermittently and are not as consistent as they are in the extreme environments. The development of resistance to antibiotics in microbes is an excellent example where an immediate effect is observed indicating the flexible nature of their genomic script (40). This type of script allows mesophiles to explore new environments with more or less similar variables and the inflexibility of script inhibits extremophiles from leaving their habitats. Both these routes of script evolution enable life to occupy the biosphere available to them completely. Are there organisms that share similar qualities of the both to an extent? Yes, but one candidate that stands out is the eukaryotic cell.

Pulse is a better engine

Life on planet earth is firmly established. A major factor in the process of establishment would be the inherent adamant nature of the genomic script. The script resists change to the maximum shifting only as a last resort. When generation of diversity results in organisms with new traits, these organisms in turn engrave the script which benefited them. They keep refining the script which leads to their increased ability in absorbing the stimuli which may be mutations or other forms of external stimuli. Increasingly resisting the change inflicted by the environment tightens the “spring”. But at a critical point the script gives in allowing the shift which releases the tension in the “spring” causing an evolutionary pulse which pushes the process of evolution forward. This process repeats itself by further generation of the pulses and depending upon favorable or unfavorable conditions of the environment at that time the results vary. What happens if a strong pulse or may be multiple

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pulses occur in a conducing environment? Such a condition probably would have resulted in diversity explosions.

The greater the strain with which an organism resists the change the better the resultant push. If it were not for this torsion of the script, evolution would yield genomically weak organisms which would be easily be driven to extinction. Moreover this friction fills every adaptable niche with precisely adapted organisms. The aptness in adaption is due to fine tuning of genomic script countering the nuances of environment. If a shift is successful the script is stabilised and engraved. The external stimuli needs to be present till the script is stabilised. But if the stimulus is lost before engraving, the script could return to its earlier state. Then again if the new shift is established the organism gains a new trait and subsequent removal of the external stimulus after stabilisation might allow the newly gained trait to act upon the environment changing or even extending it. But this type of adaption is not the aim of high order eukaryotes. Here the objective seems to be the maintenance of genome in a controlled state ensuring execution of the same script.

Scripts and evolution in tandem

Early earth probably had pocket biospheres with primitive unicellular organisms (Figure 7). The pockets as seen in the figure are the organisms along with its environment. These pockets shrunk or expanded or merged with other pockets. The major event that tipped the scale for evolution of cellular life was the formation of the ocean. This single event provided an opportunity for merging the pockets and buffering their drastically different environmental conditions. This mega event brought organisms from different environments under similar conditions. Their genomic scripts which evolved in early pocket biospheres adapted to the new environment using varied coping mechanisms resulting in generation of all the possible combinations of core cellular processes that can sustain life. This makes the

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suggestion that microbes are the guardians of metabolism to be utterly plausible (41). The scripts from the bygone era shifted to adapt to this new norm or were wiped out. The side loops or the adaptor loops would have played a major role in these circumstances. It was at this juncture that the genomic script would have diverged into path of rigidity which enabled the organism to stay with the environments similar to the early pockets or into path of flexibility which enabled them to explore the recently made available but huge biosphere of the ocean. A point to note is that the decision of rigidity or flexibility forms a pattern when different species are faced with such a situation over and over again during evolution. In meantime, hectic cellular activity caused drastic changes in the atmosphere too (42). This was another scale tipping event which threw open the land mass for future invasions.

While adapting to their environment the native organisms could have affected the formation of the localised environments. Similar to the early pocket biospheres, these pocket environment-organisms junta would have shrunk or expanded or merged. One has to keep in mind the role of the script which was continuously shifted and refined allowing the adaptation. This process would have repeated itself (Figure 7). The eukaryotic multicellular organisms might have evolved in such localised environments. Unicellular organisms evolved into multicellular life which share the characteristics of a flexible script as well as a rigid script. Was this the only way in which multicellular organisms could evolve? Scripts were shifted by testing all the possible routes and if any other route was possible then it would have been chosen. Some of these routes might have resulted in a dead end while some others proceeded towards multicellularity. These are the best possible routes that genomic script could have taken.

Early pocket environments with well adapted organisms → Merging of different pockets buffered by water → Organisms adapt their varied scripts to the new conditions → Generation of all possible combinations of core cellular process →

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Scripts diverge into rigidity or flexibility → Organisms interact with environment → New localised environments come into existence → New environment compels the organisms to shift scripts → Cycle repeats

Enabling multicellular life

When it comes to multicellular eukaryotes the script is relatively rigid. Flexible enough to respond to a few possible changes in the immediate environment. This limited flexibility is due to locking of the genome. It is interesting to note that DNA binding proteins like histones are common in eukaryotes and certain Archaea (43) which also exhibit rigidity in their script. But why lock up the genome? One reason could be that emergence of multicellularity is dependent on it. Early simple multicellular organisms would have evolved due to merging of individual scripts giving rise to a merged script which would in turn compel the constituent cells to stay together (Figure 8). Successful cellular coordination nescessary for implementing a merged script is made possible by the evolution of the communication networks. A script extends from a single genome to multiple genomes within a single cell or different cells via these networks. For example the intra-cellular coordination between nuclear genome and mitochondrial genome (44,45), cellular genome and viral genome (46), inter-cellular coordination between cells of complex multicellular organisms (47,48), coordination at cellular level between genomes of the host-endosymbionts (49,50) and host-parasite relationships. The DNA had to be bound if tight control over genome was to be achieved. Thus laying foundation for the development of complex multicellular organisms (Figure 9). The genomic script of eukaryotes branched further taking different routes. Each major route shift resulted in an evolutionary milestone. Evolution of vascular tissues in plants and evolution of exoskeleton and the endoskeleton in animals are two of the many examples.

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Click is the genomic stable state

The locking of genome suggests that evolution of eukaryotic multicellular species is a tightly controlled process which might be responsible for reduction in DNA sequence variation which results in a distinct species at relatively short evolutionary distances. A genome changes till it finds a stable state where any more change is discouraged. The genome finds itself in a stable state when environmental conditions are favourable, the side loops have adapted properly and the cell cycle goes on without a glitch. In order to move out from a stable state an external pressure or an internal need must arise. Occurrence of an evolutionary pulse might push the genome to a different state and quest for a stable state begins all over again. When this quest ends there is a high chance that a new species will be born. These genomic stable states are like the clicks of a regulating knob found on old radios for changing frequency bands or on old televisions for changing channels. When turned one can feel the tendency of the knob to snap into position with a click and It takes a nudge to move it from one click to another. Apply this analogy to the changing state of the genomes and you will get the idea.

Now consider that the change in the genome is measured on an evolutionary scale whose units are standard units for variation in genome and not time. These units are an arbitrary concept. In prokaryotes the genome holds onto its stable state over a wide range on the evolutionary scale owing to its flexible script and a free genome (Figure 10). So the “clicks” producing new species are widely spaced. On the other hand the increasingly bound genome of the multicellular organisms is prohibited to sway from its original position. Hence it occupies a short range on the evolutionary scale which allows for “clicks” with high probability of yielding a new species to occur at shorter distances. One can observe the clear consistency in species in contrast to fluidity seen in unicellular evolution. For example this has made it possible for the existence of ape and man which share striking genomic similarity

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(51) and yet remain individually distinct. High-order eukaryotes rarely change except in minor aesthetic details. If such a similarity would have existed between two species of prokaryotes it would be impossible to tell them apart. From the standpoint of evolution it can be said that all the high order multicellular eukaryotic species to be transient species but each and everyone of those is a completely distinct species.

Organism in a Click → Genome in stable state → Script generation → Script establishment → Absorbing changes → Scripts gives in at a critical point → Causes evolutionary pulse → Script shifts establishing required route → Quest for the genome stable state → Pushes the organism into another click → Driving evolution forward → New route of the script is engraved and refined → Organisms adapt to the new conditions → Genome settles in the Click → Refining of script makes it adamant → Cycle repeats and the organisms branch out.

A rigid script can translate into a flexible script and vice versa under the influence of the evolutionary pulses and clicks. Consider an environment with organisms. When a localised pocket enviroment developes within this, it influences the scripts of the organisms to shift to new routes. This might result in an evolutionary pulse. As a result genomic script might deepen the genomic stable state of the organism by increasing in rigidity and forcing the organisms to stay with the previous environment or it might lose rigidity propelling the genome to move out of the click and search for a new stable state which would result in exploration and adaptation to the new environment.

Scripts of the one-way street

Binding of the genome would inhibit script flexibility. Encapsulating nucleus reduces the genome interaction to the environmental stimulus. Further encapsulation by cytoplasm

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and cell membrane only increases this isolation. Controlled environment with only a few possible types of stimuli further ensures that the genomic script is maintained in a constant state without any unwanted shifts which reduces the possible occurrence of an evolutionary pulse to a minimum. Multiple copies of chromosomes would further ensure that the same script is executed. But this type of evolution has a drawback at the level of the organisms. If the organism is incapable of surviving in its environment it could be driven to extinction along with the responsible script. There is no possibility of shifting or readjustment of the script as was possible in the case of unicellular organisms. This one way street makes sure that only the successful script is propagated. Genomic script of any extant organism belonging to any branch on the tree of life could be successful. It does not matter from which pre-existing conditions that a successful script has evolved from. This caveat allows organisms with features radically different from one another and belonging to multiple and distant phyla to flourish within the same environment. Coexistence of such nature would clearly help in building inter-species relationships as seen in the microbial ecosystems in oceans or any of the complex animal-bacterial interactions (52,53).

A framework of genomic script

In the beginning

The central loop does not “care” about the division of the cell nonetheless it's execution is delayed by side loops till the necessary cellular function is completed which indicates that the central loop might have evolved even before cellular life came into existence in an acellular world where DNA, RNA, proteins and the viruses were the key players (54,55). The first script which became the central loop would have evolved during this era. The inhospitable early earth might have contained pocket environments which became temporary biospheres due to intermittent availability of an essential environmental factor.

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Once this factor was lost the biospheres disappeared along with it leaving behind environments which were not conducive to life. If all conditions fall into place, these “now you see and now you don't” type biosphere could be found on any planet or their moons or a comet or a sufficiently large asteroid. Possibility of some kind of favourable environment has been suggested (56–58). On early earth, this environment could have been the playground where the (((DNA ↔ RNA) ← protein) ← virus) interactions occurred giving rise to the perennial loop. Side loops are basically unnecessary for this biomolecule-bioparticle cycle. This ready-made module of a simple central loop framework could have been enveloped resulting in primitive cells. The most important consequence of cellular life would be the generation of side loops which probably evolved in parallel with the process of cellularization. In a prokaryotic world, dynamic side loops were vital in dealing with the environmental challenges. But evolution of multicellular organisms required binding of the genome ensuring controlled execution of central loop and enabling only a specific pattern of side loops.

DNA is just a physical location

The DNA, which is the physical location of the script, is distinguished with addresses at specific locations like the promoter regions. The change in these addresses could cause a shift in the script. An address change could be a change in promoter region or the regulatory networks or the super switches or genomic expression effected by the increasingly important non-coding RNAs. The first script to evolve would have been a simple script probably with the execution addresses hard coded in the DNA itself. It is possible that the first script is still active or at least exists as a relic in our genome. The genomic script with its humble beginning as a simple perennial loop has evolved into a complex entity with a barrage of side loops which still does its job in the cells of our human body. One could imagine the colossal

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size of the genomic scripts by comprehending the complex genomic machinery of regulatory networks, repair mechanisms, replication mechanisms, transcription mechanisms and the massive networks of non-coding RNAs involved in executing, maintaining and shifting them.

Why bother with scripts framework?

Genomic script framework provides a unified theme for cellular activity across domains of life. It provides solid basis on which we could understand the responses of cell. The explanations we derive from this framework compel us to view the cell with a new perspective. It may have been by chance that life hit upon this planet but it was not just chance alone that helped it survive. Unicellular organisms were fighters in every sense of the word. Every option was thoroughly verified to find the best response. If any environment could be utilized for life, it was. By doing this they tamed the planet and extended the biosphere. They were not merely constituents in the process of evolution blessed by chance opportunity rather every step of evolution was a fight won by them. This “will” to be has made the cells of the bodies, that of complex higher organisms, so resilient.

The framework of genomic script....

- *...allows for a common theme to exist for cancer.*
- *...allows for flexibility needed to counter the change in environmental stimulus in microbes.*
- *...explains microbial survival at extreme conditions*
- *...allows for complex multicellular eukaryotes to maintain their high order physiology by generation of precision.*
- *...explains binding of eukaryotic DNA and emergence of chromosomal structures.*
- *...provides better engine for driving the evolution.*
- *...allows for network of nc-RNAs and the super switches.*

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Conclusion

The framework of genomic script indicates that cancer does indeed contain few underlying principles. These principles appear to effect the functioning of genome of not only a cancer cell but a normal cell too. It is possible that different manifestations of those few principles of genomic script resulted in diverse cellular life as we know today and cancer seems to be just a type of it.

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Figures

Figure 1: Functional network of neoplastic cancer metasignature genes.

This network shows distinct sub-networks.

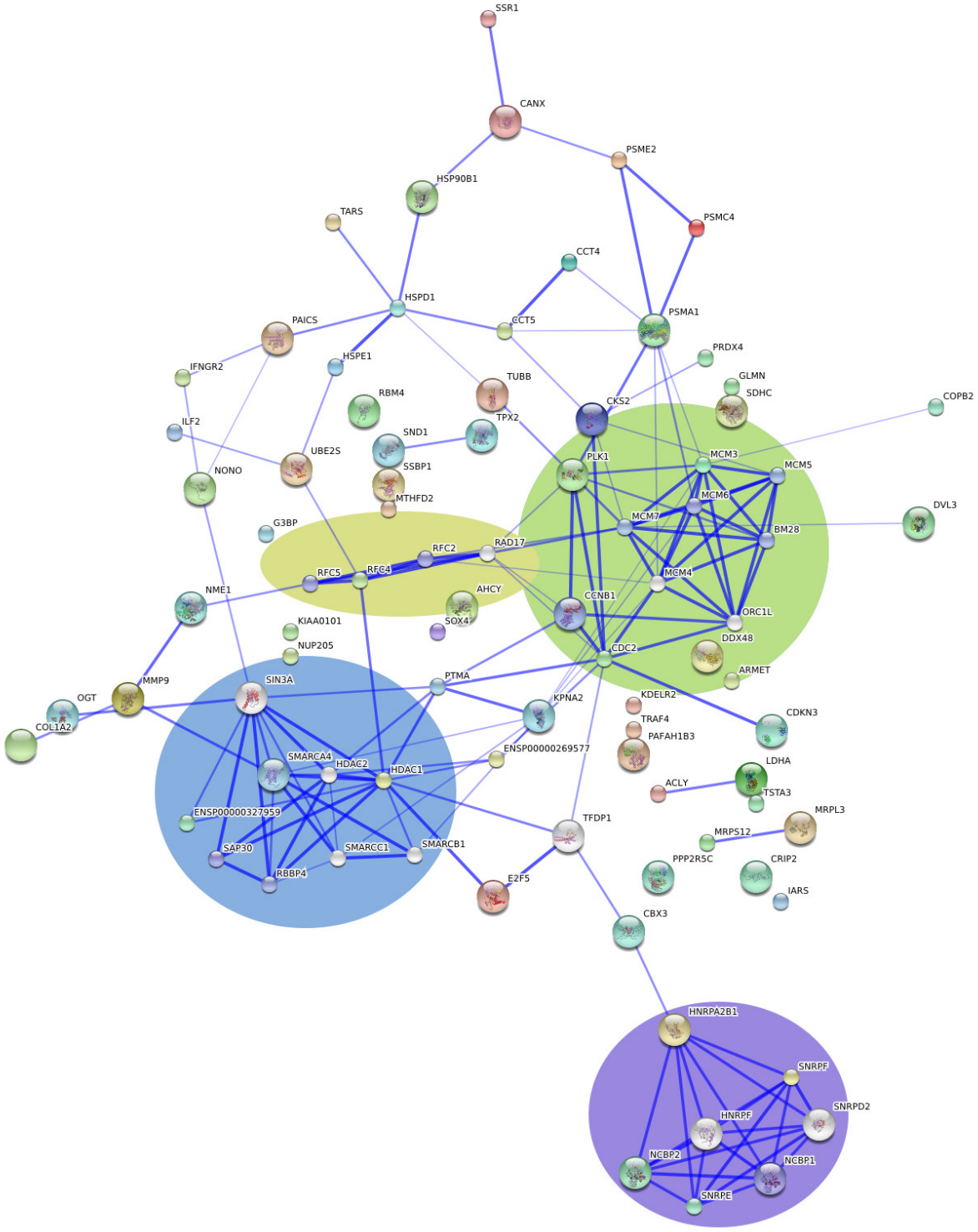

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Figure 2: Functional network of undifferentiated cancer metasignature genes.

This figure shows a cohesive central network with no distinct sub-networks.

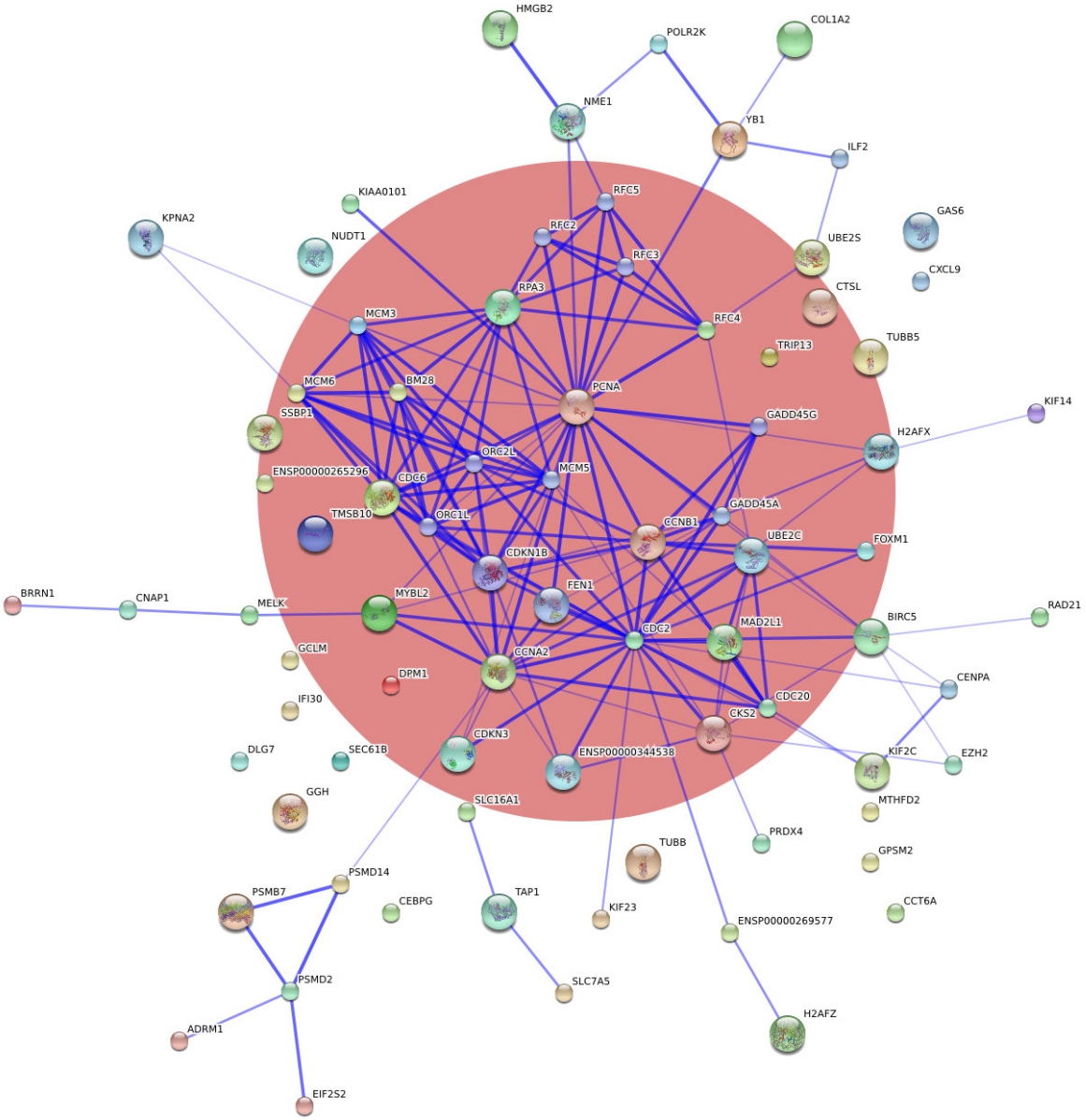

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Figure 3: Functional network of combined cancer metasignature genes.

A central network is prominent. Both lists of the metasignature genes were combined to produce this functional network. This network is similar to undifferentiated network indicating genomic favour for progression from neoplastic state to the undifferentiated.

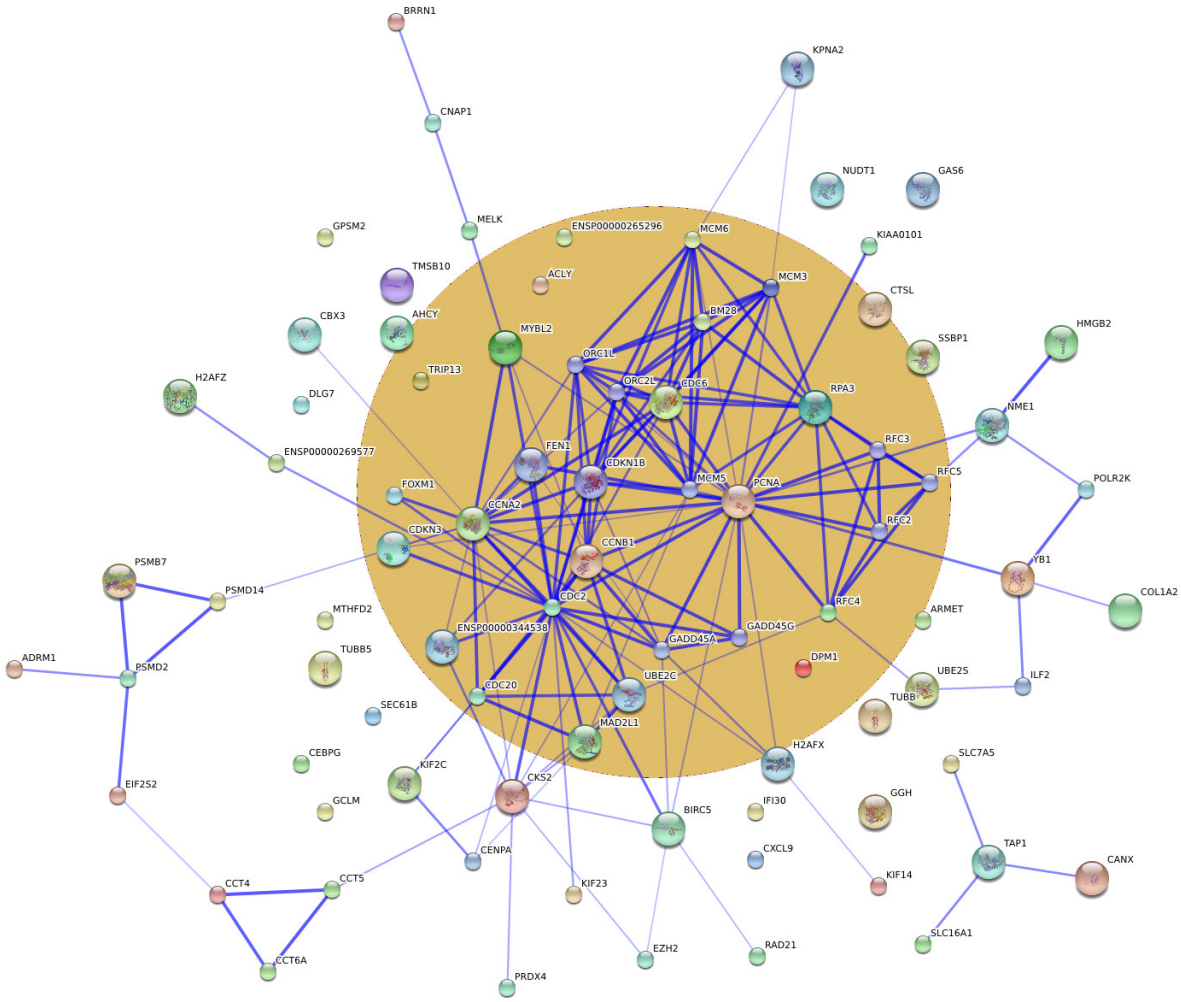

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Figure 4: Central loop execution delayed by the influence of side loops.

In functional network of the neoplastic cancer metasignature genes the side loops execute faster hence they are prominently observed but the central loop is delayed which makes it inconspicuous.

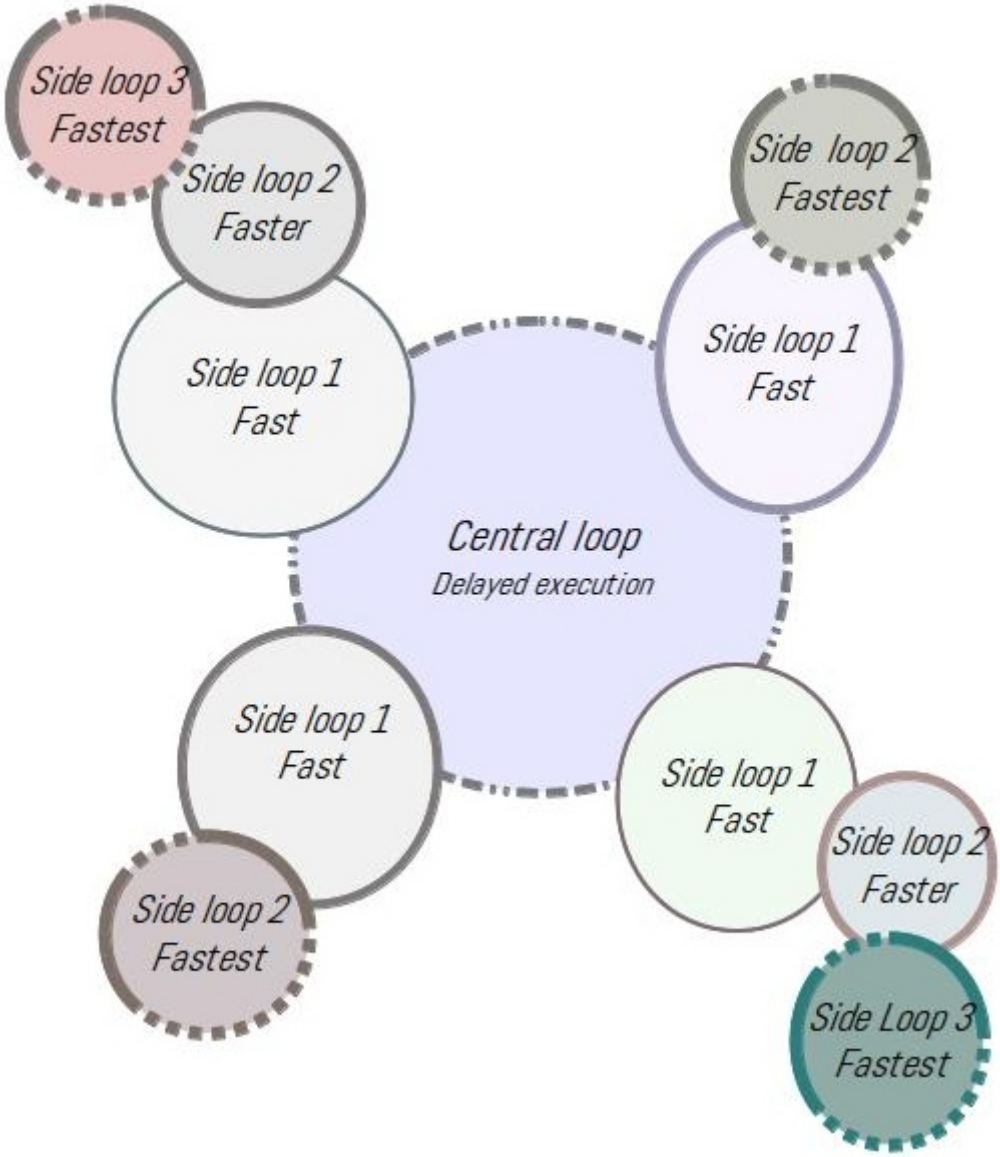

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Figure 5: Central loop executes rapidly due to weak side loops.

The functional networks of the undifferentiated and the combined cancer metasignature genes show a prominent central loop because of the inability of weak side loops to delay it. The weak side loops are obscured and the central loop is detected prominently.

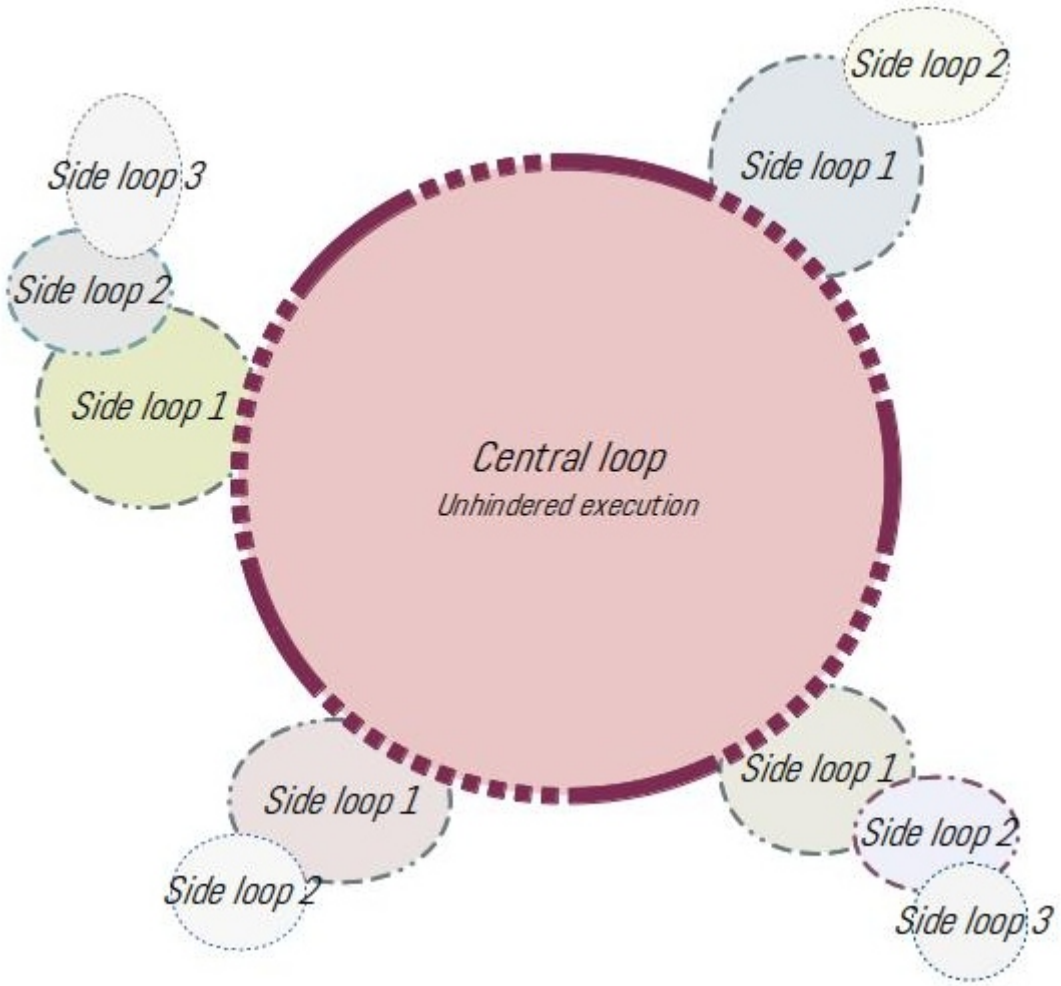

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Figure 6: Refinement of side loops halts the central loop in cell differentiation.

Each consecutive division before the cell enters growth arrest refines a specific pattern of side loops which helps to achieve precision in function yielding highly specialised cell. The side loop pattern of the progenitor cell is broken progressively in the consecutive divisions. The polishing of specific side loops is represented by thinning or the thickening of the lines which reach out from the centre to the edges of a cell.

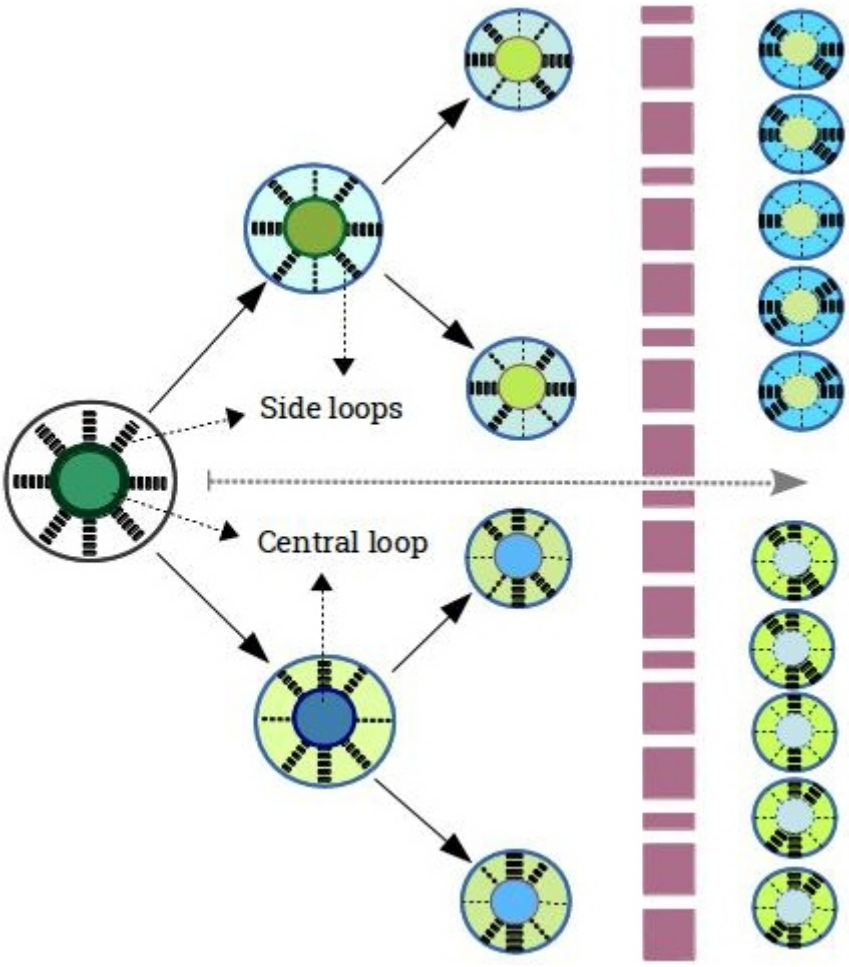

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Figure 7: Evolution and genomic scripts in tandem.

Each figure represents the total space available and the dashed boundaries represent the biosphere. Each pocket of the biosphere is the environment, the cell and the genomic script taken together as one. Sometimes environment effects the cells and cells respond with resistance by absorbing stimuli or by shifting the script. The response then effects the environment there by changing it to increased suitability to the organism. This new environment may then provide fertile ground for further evolution. ***Figure A to C:*** Early earth may have had pocket biospheres with extreme conditions. These pockets contained life adapted to the extreme conditions of the given environment. As time passed these could have amalgamated and some could have disappeared altogether. ***Figure D:*** shows an amalgamated pocket. Merger of the pockets with different conditions could have resulted in a new environment. The merger of the pockets could have been greatly helped by the formation of the first ocean which has been coloured blue in the figure. ***Figure E:*** the pocket grows large to cover most of the available space. Organisms with rigid scripts move to the edges where conditions are similar to the preceding environments. The extended biosphere gives rise to the flexible script which enables the organisms to drift off from their mother habitats and explore. ***Figure F:*** newly available environmental freedom helps cellular experimentation probably propelling the birth of multicellularity. ***Figure G and H:*** these newly evolved pockets merge or disappear or remain as they are. ***Figure I:*** the merged pocket increases in size as much as allowed. The well adapted species which favour rigidity remain confined to the edges of their environment. ***Figure J to L:*** these figures show the evolutionary process moving forward with repeating pattern.

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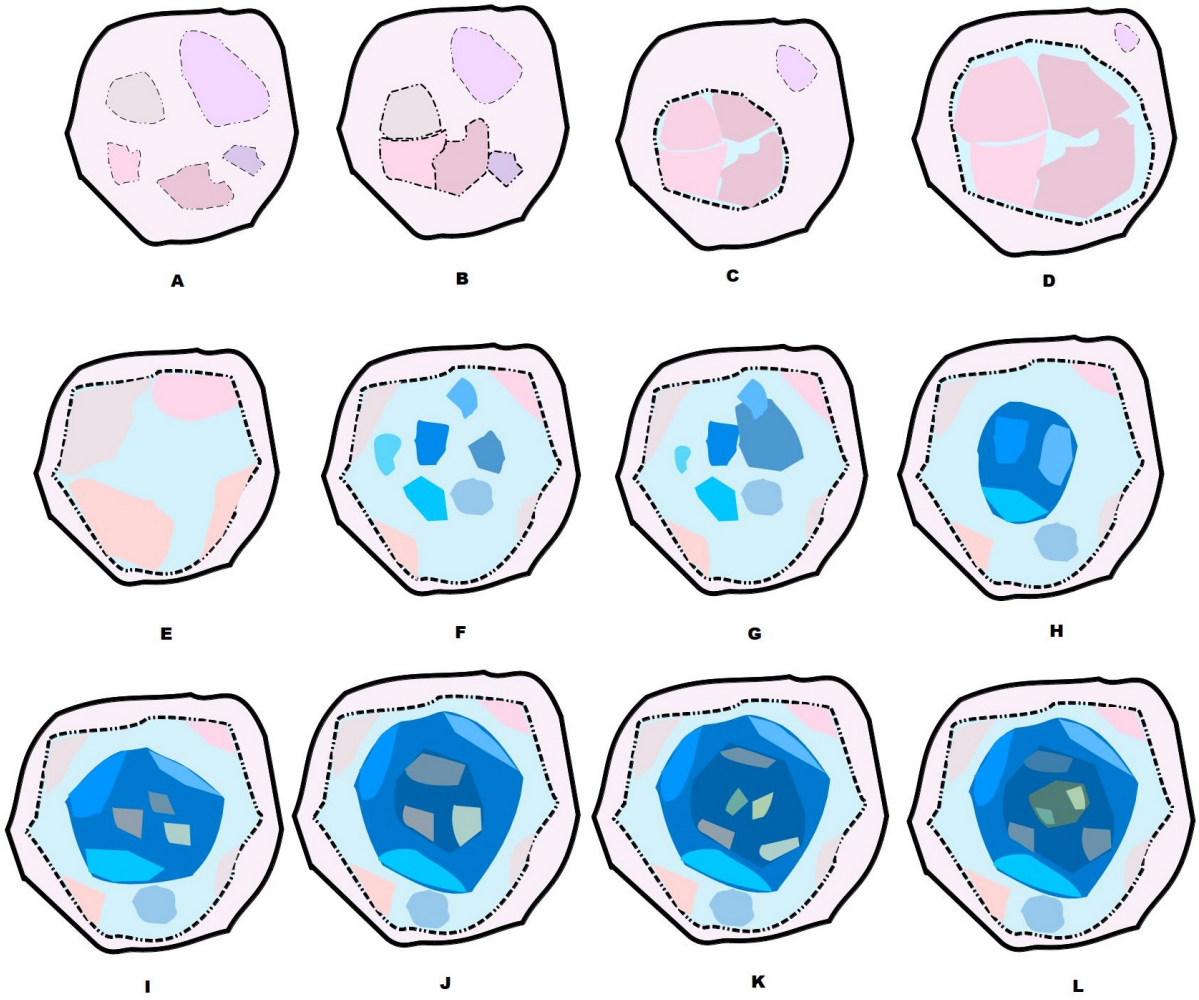

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Figure 8: Multicellular organisms evolved by merging individual scripts.

Each cell is represented by a circle and its genomic script by the outer circle of each cell. Outer circle area has been shaded in different colours indicating different scripts. Simple multicellular organisms probably evolved by merging the individual scripts of their cells. The merged script acts like a single script compelling the individual cells into multicellular coordination.

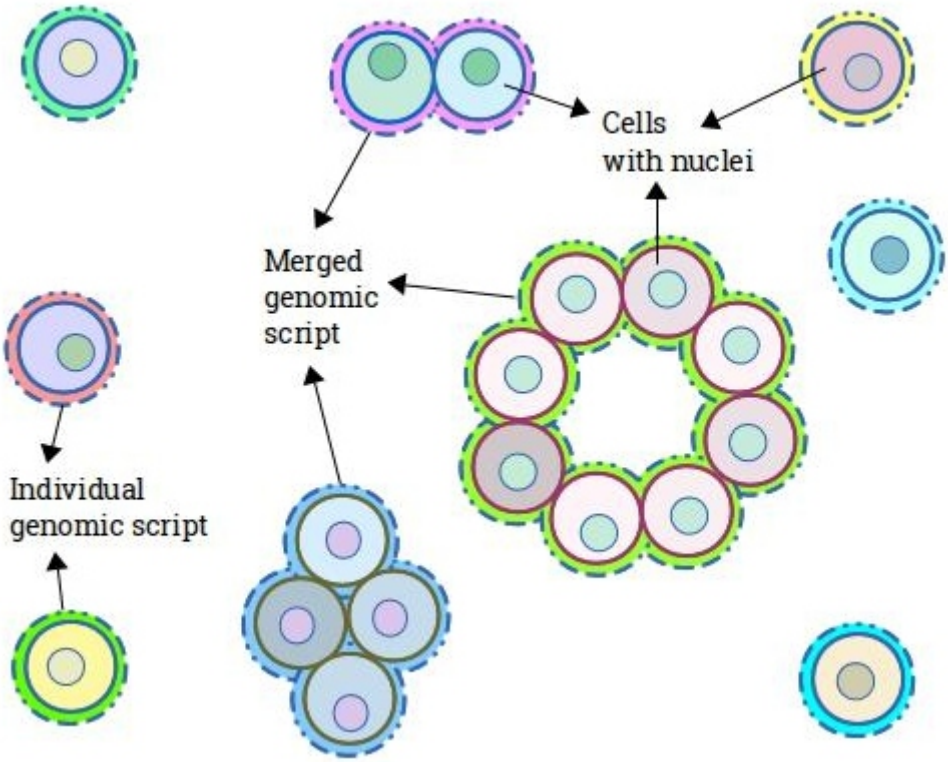

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Figure 9: Genomic script diverged into three broad routes.

The genomic script seems to have diverged into two broad routes. The first diverging point resulted in rigid scripts and flexible scripts. The rigid script is a specialist script which is perfectly adapted to the habitat whereas the flexible script allowed exploration of the available biosphere. A third route which enabled the multicellular evolution was the merger of the scripts which necessitated the binding of DNA by placing tight controls over it.

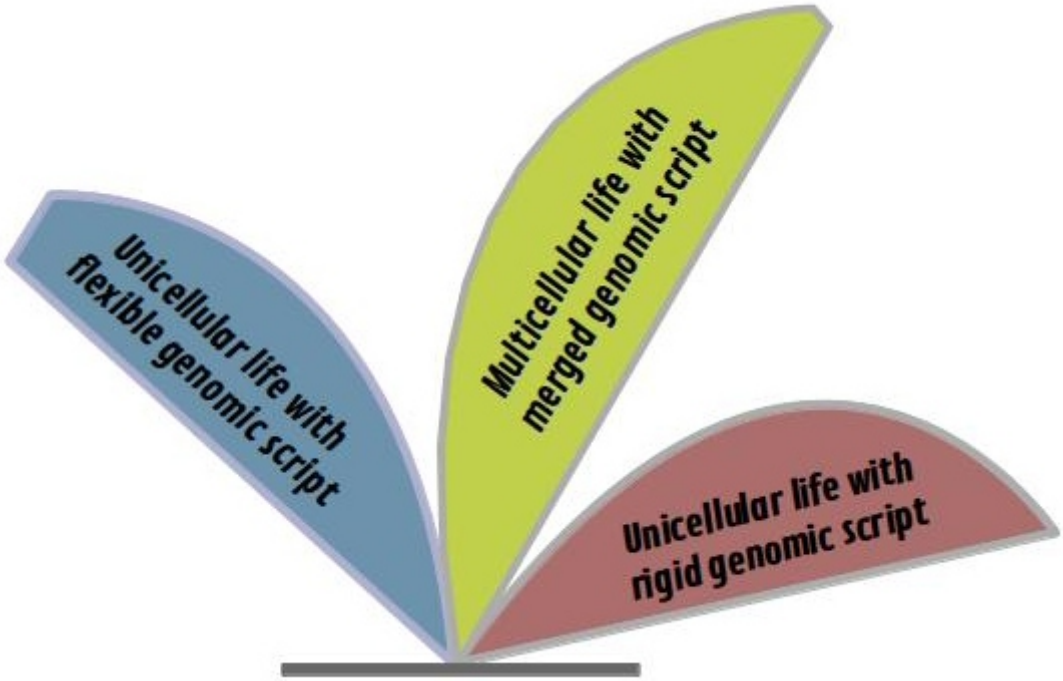

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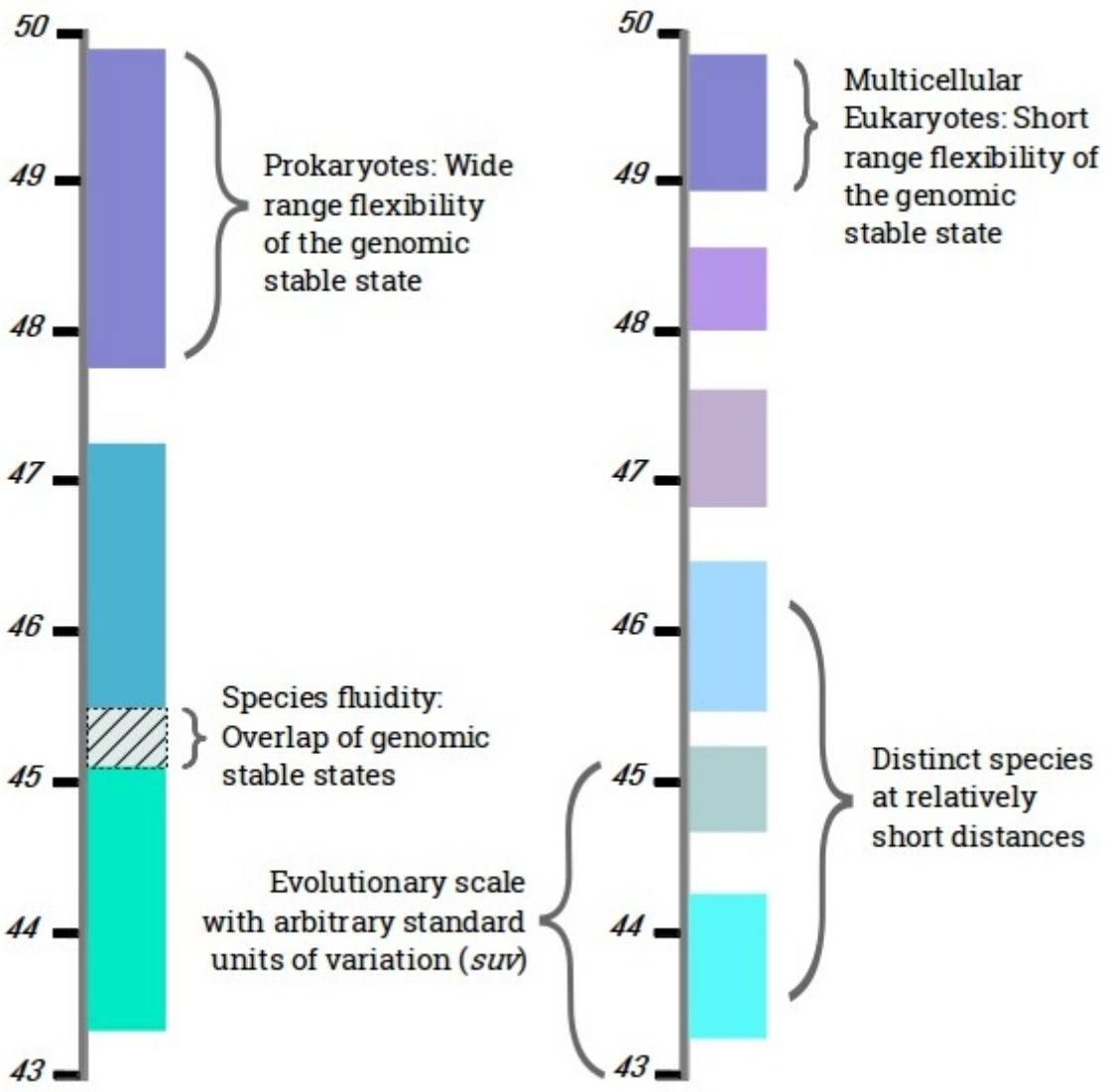
Figure 10: An evolutionary click represents the genome stable state.

The scale on the left represents prokaryotic genomic stable states and the scale on the right represents the eukaryotic genomic stable states. The scale has standard units for variation as the values. These are arbitrary and for representative purpose only. Each band on the scale represents a genomic stable state or a click where further change in the genome is discouraged. The bands are wider if the organism's genomic stable state is flexible and occur at longer distances on the evolutionary scale. The flexibility of the script enables prokayotic species to have wide clicks and sometimes two different species with highly similar genome may have overlapping stable states. In the case of multicellular eukaryotes the clicks are short and at the same time occur at shorter distances which allows distinct species to exist at short distances probably because of the tight control placed over the genome.



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