Does Collective Genetic Regulation exist?

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Does regulation in the genome use collective behavior, similar to the way the brain or deep neural networks operate? Here I make the case for why having a genomic network capable of a high level of computation would be strongly selected for, and suggest how it might arise from biochemical processes that succeed in regulating in a collective manner, very different than the usual way we think about genetic regulation.

INTRODUCTION

The operating system for Linux (the Linux kernel) is over 27 million lines. If you randomly duplicate a single line of it, recompiling it will likely result in a fatal error, so that it is no longer be a viable operating system. In contrast, if you duplicate the entire genome of many species of salamanders and allow the polyploid egg to develop [28], it produces viable individuals that are even able to produce offspring themselves. The same comparative lack of flexibility is found in most human-made technology, from cars to bicycles to digital thermometers. And this distinguishes our technology from biological organisms that show tremendous flexibility in alteration of their blueprints, yet still frequently result in a viable organism.

Is this extreme flexibility something intrinsic to biology’s basic design, or is this a property that has required evolution over billions of years? I will argue that the answer is the latter, and that this flexibility is crucial in allowing life to have evolved so many diverse and sophisticated traits, including our level of intelligence. This flexibility is closely related to the notion of genomic intelligence, the idea that the apparatus controlling the regulation of genes is performing sophisticated computations in order to evolve an organism efficiently.

This is different than genomic robustness [1, 20, 26, 27], which is the idea that the genome can withstand mutations and show little or no change in phenotype. It is changes in phenotype that lead to adaptation and increased fitness in response to environmental change. Therefore it is important to be able to produce mutations to adapt, without destroying viability in that process. That is to say, such organisms are highly evolvable [16, 23].

THE NECESSITY FOR GENOMIC INTELLIGENCE

The claim that genomic regulation is intelligent, might appear too vague to be a useful way of guiding research. Let us delve further into how exactly intelligence is being used in this biological context, and how it relates to ideas in artificial intelligence.

Intelligence can be defined as using knowledge to further goals. An example of neural intelligence is to use the pattern of photons impinging on one’s retina to determine that a tiger is coming towards you, and that the best course of action is to run away. The way that we identify patterns is largely through learning. We are given many examples of patterns and are often told of their classification, say, tigers, bicycles, and cars. These are examples of “supervised learning” [14]. Let us try to determine if there is a genomic analogy to this kind of learning.

Instead of inputs being visual patterns, the genome will have a large number of external inputs from cell signals such as growth factors (receptor tyrosine kinases), ion channels, or adhesion sensing [6]. The information from these signals is communicated to the nucleus. This changes its state, causing it to alter the outputs of this process, that is the proteins being produced. This can tell the cell, for example, to stop growing or to form a synapse with another cell. There is a lot of regulatory machinery in the nucleus that is computing these outputs.

This has a fairly close analogy to the way the brain, or an artificial intelligence (AI), learns patterns such as described above [14]. The difference is that there is no direct supervision going on. The inputs are given, but it is not obvious how the cell is supposed to know the expected outputs.

In principle, evolution will eventually be able to adjust regulation so that outputs correctly match the inputs. Mutations of the genome will alter the proteins that are produced in response to a given input. These can cause developmental changes and thus changes in the developed organism, affecting its fitness. This will cause an evolution towards fitter cell outputs. But this is a much more indirect and therefore inefficient process than what can be achieved with supervised learning. Hence evolution through genetic change would appear to proceed through a much less efficient algorithm than what is achievable through supervised learning algorithms such as are employed in AI.

From experience with human made designs, the most difficult hurdle to overcome is the lack of robustness. If
99% of the time a mutation is lethal, it makes evolution inefficient. If instead, mutations cause tiny effects, then although an organism might be viable, it will be functionally almost identical to its progenitor. This would be a problem associated with inflexibility. What is needed is intelligent genomic regulation, where even with large changes to inputs, the outputs will be different but not in ways that cause the organism to fail at development, thus allowing the potential for many more beneficial mutations.

When the genome mutates, new patterns of signals impinge on the cell (as well as the possibility of new kinds of protein signals). The genetic network must be able to generalize well so as to respond efficaciously to these new signals. And not only must the genome respond to mutation, but to different gene alleles that occur with sexual reproduction. Intelligent responses would also allow for much improved regenerative capacity [2].

But this kind of intelligent regulation as described, is not an example of supervised learning, because there is no cell training where desired cell outputs are given. Instead the cell likely uses an empirical approach, using signals impinging on it, and learning how actions that it takes affect the environment around it. This is quite similar to a well known technique in AI, reinforcement learning [35].

Regulatory feedback goes far beyond the nucleus including signals coming from other cells. If a mutation has had a positive effect in some respects but has caused a side-effect, for example a decrease in cell adhesion, this can be signaled back to the nucleus and the genetic network can compute what measures are necessary to ensure cells are correctly bound together. What is important from the standpoint of evolutionary efficiency is allowing certain changes to happen without destroying the viability of an organism. For example, mutations leading to greater intelligence are difficult for a number of reasons. Blood supply must be increased, the skull must also expand, but more importantly, there is an incredible complexity involved in neural processing, and small changes would be lethal for most architectures (such as the Linux kernel) without very sophisticated rules for how development should proceed. If all of the components needed to co-evolve require separate mutations, this would tremendously stifle the possibility of useful genetic changes. Instead there is likely a great deal of intelligence applied in the way say, angiogenesis or neural growth, progresses when tissue receives signals that require it.

The above argument concerns genomic intelligence to allow for biological flexibility. But a smarter genome will speed up evolution in other important ways. Intelligent agents use the past to better predict optimal future actions to take. The genome does not have a direct record of its ancestor’s history. It does not know directly if there had been a prior ice age that appears to be re-emerging again. But it does contain a great deal of spare capacity to store away information from previous generations, that can then be used in development [13]. For example, if there is a change to the environment, say a drop in average temperature, a mutation can switch on a gene that grows hair. The process of growing hair does not need to re-evolve from scratch. This example has no concept of directionality or ordering in time, just that there are useful genes that can be turned on, if needed. However accessing the timing of previous genetic changes gives the genome the opportunity to better predict and optimize developmental response. The study of heterochrony [17], how timing in development is influenced by evolution, shows that the genome does indeed have access to some, admittedly crude, approximation to the order in which genetic change happened.

Therefore the genome can utilize information about its present and past states, to make decisions on how to develop. For example, a gene to suppress the production of hair may be able to access the fact that its recent ancestors appear to have a tendency of becoming less hirsute. This would suggest to the genomic network that a mutation to suppress hirsuteness have its effects enhanced, creating an acceleration in evolution of a hairless phenotype. Although directed mutations are not normally possible from a physical perspective, processing of past information contained in the genome can lead to similar evolutionary behavior.

The above discussion illustrates that a highly intelligent genome, capable of performing complex prediction and inference, allows an organism to respond to change more efficiently than one’s with lesser computational sophistication. Evolution of such complex genetic regulatory machinery will then make an organism more highly evolvable [23, 34]. It would appear likely that such machinery has been selected for, and is why biology contains the tremendous flexibility in development discussed above, in comparison to human technology. Despite the vast amount that we have learned from evolutionary developmental biology, this view does not appear to be widespread. Evolvability has been studied extensively [16, 23], and a large number of traits associated with it have been studied and described. For example, weak linkage [4] (e.g. between different cellular processes), exploratory mechanisms (e.g. adaptive immunity), and genomic compartmentation [34]. All of these traits are logical guidelines you would also expect in a complex human designed machine, or software, that was built to be upgradable. But these guidelines are not nearly enough to actual build the algorithms necessary for the machine to function. The necessary feature for evolvability is intelligence.

This then begs the question, of how the genome would be able to perform this level of sophisticated computation, which I turn to now.
MECHANISMS FOR COMPUTATION IN THE GENOME

Only about 3% of the genome is translated into proteins. Yet until recently, it was only these portions of the genome that were considered as having an important biological function. A great deal of recent effort has been devoted recently to studying the function of the other 97%, and it has been shown to have a very large number of functions [7, 31]. However given the amount of DNA, and the complexity of its functions, it is still far from being well understood. Because this DNA is not directly producing proteins, its function will be to regulate the gene-coding portions of the genome. This gives the genome a much larger amount of information to utilize in computation and potentially lead to much more complicated regulatory mechanisms. This brings us now to the heart of this discussion: is gene regulation related to AI?

We now are living at the beginning of a new age in computer science, where software and hardware utilizing “Deep Learning”, or artificial neural networks [9, 18] has outstripped older methods in machine learning. Could similar ideas be important in the way that the genome performs regulation?

The distinguishing feature of this kind of architecture, is that computation is done collectively, with many inputs impinging on a single element, like that of a neuron. This idea dates back to 1958, which is when the “perceptron” was invented [24], and gave rise to work in connectist models, which essentially stack perceptrons to create more powerful learning algorithms [21]. These models have now solved problems that had hitherto been considered intractable, such as speaker independent speech recognition [8].

This biologically inspired architecture is much more general and simpler than the earlier and more traditional rule based approaches. Instead of attempting to hand-code the architecture of a task, such as translating French into English, English sounds are given as inputs, and French as outputs [8]. The strength of the connections are algorithmically adjusted until the network has learned the task.

The distinction between the traditional rule based algorithms, and deep learning, is the idea of collective computation. A single connection between two neurons, is serving many simultaneous functions. Its purpose is manifold. It is only when combined holistically with the other neurons and connections, that a precise computation emerges. Single connections can be severed, and this normally has little effect on performance. In this way, neural network models are robust. In contrast, a traditional digital circuit, or the source code for the Linux kernel, is extremely fragile.

Genetic regulation is traditionally thought of as a network of regulatory elements that can for example, enhance or silence, transcription of their associated genes. It is often considered to be boolean and behaves similarly to traditional digital circuits, for example AND and NOT gates. There is little doubt that this kind of regulation plays an important role in gene regulation and evolution [30]. However, it is the purpose of this section to point out that the other 97% of our genome, does not fit neatly into this traditional picture, and can potentially be used for collective regulation which would share many features in common with collective computation, like Deep Learning. It has the potential for greatly increasing the intelligence of the genome, and therefore would be evolutionarily selected for. Analogies with connectist models have been proposed several decades ago [22].

Non-coding RNA (ncRNA) is expressed with an abundance of about one tenth that of mRNA, but this depends strongly on cell type [3]. Physical arguments [10] give a collision time between different ncRNA of approximation 0.25s. But the half-life a ncRNA in the nucleus is of the order of 30 minutes [19]. Therefore there is plenty of time for ncRNA to interact before being degraded.

It is possible [10] to come up with a theoretical analysis of how interactions between the RNA molecules, and a mechanism for their creation and degradation, can map onto a model of collective computation, such as a Boltzmann machine or Hopfield model [15, 25]. The features of this model are as follows

a The equilibration of N different RNA species that undergo pairwise binding and unbinding to each other with a set of equilibrium constants. At one time, some fraction of every species will be bound to another RNA molecule.

b A creation rate (due to RNA polymerase II) for an RNA species that depends on the fraction of bound to unbound RNA for that species.

c Degradation of RNA on a much longer timescale than than the interactions between the RNA molecules.

The interaction strengths between any two RNA molecule are weak and they bind promiscuously to each other. By adjusting the equilibrium constant for binding, the system can evolve to have an arbitrary relationship between input signals and the outputs that are produced. The inputs to cells through signalling will affect concentrations of RNA molecules in the nucleus, this is then processed by the above mechanism, to produce output mRNA molecules that will then be transcribed to proteins. Item b above specifies a creation rate as a function of bound to unbound RNA. This function is required to have a particular kind of sigmoidal shape in order for this model to map onto a neural network model. There is evidence that this kind of creation is sometimes utilized by noncoding RNA [30, 32, 33].
The basic framework for regulation of this kind, is that there is a lot of weak binding and unbinding between different biomolecules in a cell's environment. The sum total of these interactions would seem to serve no useful purpose. However coupling this with a creation rate that depends on the bound fraction of such molecules, can in principle, perform sophisticated collective computation.

This particular model is unlikely to be precisely what is found in the cell nucleus. However it points out that there are mathematically viable mechanisms based on the known molecular biology of the cell that can in principle perform sophisticated gene regulation.

One of the arguments that has been used to dismiss the 97% of DNA that is non-coding, is that it is often not evolutionarily conserved. In comparison with traditional regulation, this collective mechanism is quite robust to mutation [10]. Therefore one would expect that to optimize evolution, a much higher mutation rate is desirable as is often seen for non-coding RNA [5].

**DISCUSSION**

Unfortunately at the moment, there is no strong evidence for collective regulation. There is evidence for some of the pieces, such as extensive RNA-RNA interactions in humans [29], that can detect the formation of inter-RNA duplexes, stronger interactions than would be optimal for the weak interactions described above. But the general mechanism described to achieve collective regulation could in principle be accomplished by a large diversity of different kinds of molecules, including proteins. Weak interactions combined with control over creation rates are the main two requirements.

Genome wide association studies are widely used to understand the genetics of a large variety of diseases. It has already become clear that single genes cannot predict risk, and instead this is controlled by a large number of different regions, 90% of these are non-coding regions [11, 12]. This is circumstantial, but hardly compelling evidence for regulation being collective.

Biologist are very good at finding specific biochemical interactions and have uncovered an enormous amount about regulation of the genome. However it would be much harder to make sense of thousands of interactions simultaneously to try to uncover a new deep-learning-like mechanism for genomic regulation. However it is argued here that this sort of architecture is plausible biochemically and would be selected for evolutionarily. Therefore it deserves some effort to try to devise experimental methods to test for it. If collective regulation turns out to be key, this will have significant implications for the future direction of a lot of research. This would have scientific benefit not only in biology, but inform us on how to design more flexible software and hardware.

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