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Reply to comments

Implications of the Read–Write Genome view

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I am pleased to see that commentators from such disparate backgrounds (genomics, physiology, cancer research, evolutionary computation and physics) agree that there is benefit in rethinking the genome as a RW memory organelle under cell control [1]. This agreement indicates that the RW Genome will prove fruitful and adaptable to many areas of the life sciences and possibly even to the hard and information sciences as well. There are also dissenting interpretations.

Let us deal with the dissents first and then move on to further implications of the RW Genome view.

While grudgingly acknowledging at the end of his comment that "genomes are indeed read–write", molecular geneticist Damon Lisch repeats quite a few of the standard (and easily rebutted) objections to the idea that cells actively engage natural genetic engineering (NGE) for useful genome inscriptions to cope with episodes of evolutionary challenge [2]. This is surprising, coming from the author of a paper on the action of maize transposons in "directional modification of genes through biased insertion and DNA acquisition" [3].

A single example will illustrate the limitations of Lisch's reservations. He characterizes mobile genetic elements (MGEs) as "selfish" "parasitic entities" and states, "it is extremely unlikely that any but a tiny fraction of the insertions contribute to meaningful differences in the morphology of related species". What Lisch considered "extremely unlikely" is now established genome science. He failed to notice that I indicated where we do have **minimum** quantitative estimates of the contributions of MGEs to functionally usefully genome elements in mammals. Last year, these stood at 280 000, or 19.1% of all conserved (i.e., positively selected) differences between eutherian mammals and marsupials [4]. Moreover, MGEs have been identified as contributing to between 11 and 20% of human regulatory elements [5].

In a similar dubious vein, Maxim Frank-Kamenetskii argues that the examples of genome RW character do not invalidate the "universal" principles of conventional views about genomic information [6]. I have to disagree strongly on two grounds. In my understanding of the last 60 years of molecular biology, the data show that genome inscriptions are the rule, not the exception. Empirically, the evidence of genome inscriptions needed for progress through the cell cycle, multicellular development, and evolutionary innovation overwhelms any claim that they are exceptional, rather than fundamental, events. From an epistemological perspective, I further find it impossible to accept "universals" where there are well-documented counter-examples [7]. Our job as scientists is to formulate our theories to incorporate

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new and unpredicted data without having to make special exceptions. History has shown that accounting for the exceptional results lead us to deeper, more comprehensive formulations.

Paul Davies comments at length on the relationship of a rewritable genome to the problem of cancer cell formation and tumor progression [8]. My own thoughts about how cancer relates to genome rewriting include the following points:

1. Cancer provides us with an opportunity to observe genome rewriting in an accelerated real-time context. Both epigenetic remodeling and DNA structural changes occur rapidly in tumor development. Since, as Davies indicates, tumor development has so many parallels with embryonic morphogenesis, we have an opportunity to learn (and, hopefully, apply therapeutically) basic principles of genome writing. Of particular interest to me are observations that indicate regularity in natural genetic engineering (NGE) of chromosome structure at so-called "fragile sites" [9], exemplified by repeated appearance of the Philadelphia chromosome in chronic myelogenous leukemia [10].
2. The fact that genome restructuring functions are under cell regulation (largely epigenetic) provides an alternative way to think about the origins of cancer. Rather than resulting from an accidental mutation, cancer may well begin with an event (at the nucleoprotein, epigenetic or DNA level) that subverts the normal controls over cell proliferation and/or NGE. Disruption of control circuits helps explain (a) why certain carcinogens have nothing to do with DNA damage [11] and (b) why tumors display increasing genome instability (i.e., greater NGE activity) as they progress.
3. At advanced stages of many cancers, we see extreme examples of NGE activity, such as chromothripsis (fragmentation and scrambled reassembly of individual chromosomes) [12]. Elucidating these extraordinary cases of genome restructuring in real time will teach us important lessons about what DNA transformations may have occurred at periods of evolutionary crisis.
4. The redirection of morphogenetic functions in cancer that Davies points out provides us with an opportunity to learn more about the potential operation of cell circuitry in targeting the action of NGE operators. Are the observed genome changes simply the result of selection for more rapid proliferation (conventional wisdom), or do they reflect biases in rewriting the genome towards having a particular functional architecture (the RW Genome view)? I favor the second possibility because of the predictability of the characteristic progression profiles displayed so many distinct kinds of tumors. This predictability underpins the hoped for clinical utility of tumor genomics [13]. Uncoordinated changes and selection for rapid proliferation would not be expected to produce the observed regularities.

Larry Bull, a computer evolution researcher, draws some important parallels between the RW Genome and *in silico* information processing [14]. He confirms the essentiality of a Write function to universal computing machines, and he points out the value of "embedded change/search heuristics" to *in silico* evolution procedures. It is particularly noteworthy that he emphasizes the ability of systems with these capabilities to deal more efficiently with constantly changing selective environments (such as living organisms confront) as well as increased evolutionary capabilities conferred by combinations of differentiated and communicating cells. As he points out, it will be fascinating to see how far new ways of viewing biological evolution impact, and are impacted by, their applications to evolutionary computation.

Another evolutionary computation scientist, Chrisantha Fernando, also sees the value of parallels between the RW Genome viewpoint and artificial intelligence (AI) systems [15]. Fernando provides us with some very instructive examples of *in silico* systems that may provide instructive models for biological experimentation. My main quibble is with the statement about the nature of intelligence that may act upon the genome: "Intelligence is defined by Turing award winner Allen Newell as using existing knowledge to make the best decisions in the current environment... In this sense, Shapiro is literally claiming that genomes are intelligent". Fernando makes a common error here. I do not ascribe any kind of cognitive agency to the genome itself. A computer drive stores but does not execute programs or routines; likewise, the genome is simply a storage device (albeit one of amazing versatility and sophistication). Agency to generate changes quite specifically belongs to the cell or to intercommunicating groups of cells. As I pointed out in my rethinking of Crick's Central Dogma, DNA is inert if it does not interact with other cell molecules [16].

As a physiologist, Denis Noble naturally endorses the cell-active view of genome rewriting [17]. He cites his own paper on biological activities in evolutionary change [18] and points us to longstanding literature on cellular control over genome function in developmental biology. He emphasizes the roles of the cell and host organism in determining

genome-encoded phenotypes. In this context, it is worth repeating that there are no examples of genome functionality outside of a cellular context. Recent hype about the creation of "artificial life" by Craig Venter and colleagues, for example, fails to recognize the inconvenient realities that (1) the copy of an existing genome had to be transplanted into an already existing cell [19] and (2) living yeast cells were essential contributors to assembling the genome copy [20].

I find it interesting that it is the physicist Robert Austin, not a biologist, who points out the limitations of the ROM Genome view of evolution [21]: "... selection is not evolution, as Fisher said... Natural selection provides a framework for how changes in the inheritable material can be culled via competition amongst individuals, but the creative generation of the mutations comes from evolution, the sculpting of the genome upon which natural selection acts". The creative acts in evolutionary change lie in the province of Variation. Natural Selection, as envisioned by Darwin and Wallace, is a *post hoc* test of whether the genomic changes provide adaptive benefits. Wallace, in particular, viewed the purifying action of selection as a stabilizing rather than a creative force, comparing it to the governor on a steam engine [22].

The mathematical biologist Michael Deem points out how well genomic observations of combinatorial changes in evolution fit with predictions and models from the 1970s up to the present day [23]. Deem emphasizes the theoretical superiority of a hierarchical search strategy based on combining useful genomic modules over random walks through genome space for generating DNA capable of encoding adaptive novelties. For this reason, he embraces the complex and multivalent modularity of genomes over the view of a collection of well-defined genes restricted to a small number of defined functions and modes of expression. As one of his papers concluded a decade ago [24], Deem concurs that evolvability is itself an adaptive function.

Finally, although he is in overall agreement with the transition from a ROM to a RW view of the genome, the bioinformatics specialist Eugene Koonin puzzles me with his insistence on the stochastic nature of DNA change [25]. His comments on this point strike me as somewhat self-contradictory:

"To justify the RW metaphor, it is necessary to show that the genome systematically sustains changes that are "programmable", i.e. directed by the cell in response to internal or external cues... genomic changes are mostly stochastic but are induced by environmental stimuli and enhance the organism's adaptive capabilities... Many if not all organisms appear to possess specific functional systems that actively promote evolutionary change, i.e. evolvability appears to be evolvable."

Determining the extent of regulated versus stochastic changes is precisely the research agenda I suggested at the end of the review. The stochastic component may be far lower than Koonin states. There are many possible situations that lie between a strictly stochastic process and rigid determinism. Highly functional immune system DNA rearrangements illustrate this point very well. In immunoglobulin-encoding DNA segments, cutting, splicing and somatic hypermutation events are tightly targeted, but they are combined with several essential diversity generators (combinatorial diversity, junctional diversity, and untemplated *N* region diversity) (http://www.huffingtonpost.com/james-a-shapiro/genetic-engineering-immune-system-evolution_b_1255771.html). These are necessarily diverse and indeterminate events, but they are far from stochastic. They occur in a special class of differentiated cells in a determined order at specific sites in the genome.

Whether cells carry out an "informed" or blind search of genome space by NGE is a key issue to be resolved in this century. My own expectation is that we will be surprised to find out how frequently hybridization- or stress-induced DNA changes prove to be functionally relevant. I base this expectation on the knowledge that surprises in science are nothing new. After all, one synonym for "surprise" is "discovery".

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