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Applications of Artificial Life and Digital Organisms in the Study of Genetic Evolution

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Abstract

Testing evolutionary hypothesis in experimental setting is expensive, time consuming, and unlikely to recapitulate evolutionary history if evolution is repeated. Computer simulations of virtual organisms, also known as artificial life or digital organisms (DOs) can be used for *in silico* study of evolutionary processes. This mini-review focuses on the use of DOs in the study of genetic evolution. The three main areas focused in this review are (1) emergence of specialized cells, (2) chemical and environmental resistance, and (3) genetic adaptability. This review concludes with a discussion on the limitations on using DOs as a tool for studying genetic evolution.

Keywords: *Digital Organisms, Artificial Life, Evolution, Genetics, Robustness, Mutations.*

1. Introduction

Nothing in Biology makes sense except in the light of Evolution -- Theodosius Dobzhansky [1]

Nothing in Medicine makes sense, except in the light of Evolution -- Ajit Varki [2]

Evolution is a fundamental aspect of biology. However, testing evolutionary hypotheses in an experimental setting poses many challenges [3]. Firstly, it is highly time-consuming due to long generation time associated with most species. The longest on-going laboratory experiment in evolutionary biology have been initiated by Richard Lenski in 1988 [4], using a common intestinal bacterium, *Escherichia coli*, which has one of the shortest generation time. Other experimental evolution experiments [5-8], such as adaptation to salt and food additives, have also used *E. coli* due to its generation time. Secondly, it is generally prohibitively expensive to examine the genetic makeup of each bacterium using experimental techniques, such as DNA sequencing. At the same time, such examination is destructive in nature and the examined bacterium cannot be revived for further evolutionary experiments. Thirdly, a number of interesting evolutionary questions, such as questions pertaining to social and sexual behavior, are impossible to experiment on. Lastly, it is impossible to experiment on the effects of extinction [9] or to recapitulate evolutionary history as Stephen Gould [10] had argued that the outcome of life, both general and in detail will be very different from what we have today should evolution be repeated again.

A means around these limitations is to use models of bacteria or higher organisms, rather than real biological organisms. Using concepts of cellular automata, Christopher Langton [11] showed that modeled organisms behaved in a life-like manner in a virtual reality world employing fundamentally life-less chemical concepts. These modeled organisms are known as artificial life or digital organisms (DOs) which organisms are simulated, mutated, and reproduced in a computer [12]. Although digital organisms are not real biological organism, it has characteristics of being a real living organism but in a different substrate [13]. Batut et al. [3] argue that DOs is a valuable tool to enable experimental evolution despite its drawbacks as repeated simulations can be carried out with recording of all events. Furthermore, only computational time is needed to study every organism, which is analogous to sequencing every organism as complete “fossil record” can be maintained in the hard disks [14], and this process is not destructive in a biological sense as the studied organism can be “revived” for further simulations.

Hence, DOs present as a potential tool for *in silico* study of evolutionary processes [3, 15]. Although DOs have been used in non-biological areas of study [16], this mini-review focuses on the use of DOs in the study of genetic evolution. The three main areas focused in this review are (1) emergence of specialized cells, (2) chemical and environmental resistance, and (3) genetic adaptability.

2. Emergence of Specialized Cells

The emergence of specialized or differentiated cells from a lump of undifferentiated cells; thereby, forming specialized tissues and organs, is crucial in multi-cellular organisms. Without specialization, multi-cellular organisms will be nothing more than a lump of homogenous cells. Using DO, Willensdorfer [17] examines unspecialized to specialized cells transition and suggest that the success of evolving specialized cells is proportional to the size of the organism and describes the model for this transition [18]. The reason is that a larger homogeneous organism, which comprises of more cells, is able to afford a higher failure rate in the evolution process compared to a smaller organism. This work is extended [19] to examine germ cell specialization from somatic cells using DO. Their work [19] suggests that a fraction of homogeneous cells exhibit higher mutation rates and losing reproductive potential to be somatic cells, while the rest of the cells maintain reproductivity as germ cells. Goldsby [19] term this division of labour [20] as "dirty-work hypothesis" as the process of specializing into metabolically efficient somatic cells is likely to result in more detrimental mutations while leaving the germ cells genetically pristine with lowered mutation rates.

Evolving specialized cells is advantageous as Furusawa and Kaneko [21] demonstrate that a complex multi-cellular organism containing a variety of specialized cells can be achieved using cell-cell interactions and does not require complex control mechanisms. Moreover, larger growth rate is achieved by cooperative use of resources compared to a lump of homogeneous cells [21]. This may also suggest that evolution promotes the emergence of specialized cells, especially in a resource scarce environment [22].

Basanta et al. [23] examine the organization of multi-cellular organisms in a virtual environment and discover that tissue structure can be maintained through a variety of strategies. However, there is no selection on tissue organization in their work [23], suggesting that tissue organization is likely to be a by-product of morphogenic evolution.

3. Chemical and Environmental Resistance

The adaptability of chemical and environmental stresses is important for the survivability of a species [24]. A form of environmental stress is resource limitation. Johnson and Wilke [25] examine a predator-prey system, which is one of the two standard resource limitations [26] using 2 populations of DOs whereby one species prey on the by-product of the other, also known as resource cycles. Their work [25] suggests that the abundance of the 2 populations is out of phase by exactly a half cycle. This suggests that mutually dependent populations are able to synchronize the population sizes to adapt to limit the impact of resource pressures. In turn, this leads to ecological evolution seen in a population of DOs [27] where there is a tendency for shorter resource cycles and the evolution of cooperative resource use strategies.

Yedid et al. [9] focuses on the re-emergence of complex traits after mass extinction process, which is simulated by DOs as a means to examine evolutionary resistance to catastrophic events. Their results [9] suggest that re-emergence of extinct complex traits is dependent on many factors, including the genetic history of the organism and the ecology post-extinction event. Further work on different extinction regimes by the same group [28, 29] suggests that the diversification of survivors after mass extinction events is significantly affected by the genetic history of the survivors. These studies [9, 28, 29] suggest a complex interplay of the nature of extinction events, the genetic history of organisms, and the ecology post-extinction.

Resistance to antibiotics is a serious medical and social problem and studies suggest contradictory findings on the loss of antibiotic-resistance after disuse [30]. Using DOs, Castillo and Ling [31] examine the loss of antibiotic-resistance during antibiotics disuse in event where no fitness cost for maintaining resistance. Their results [31] suggest that complete elimination of specific antibiotics resistance is unlikely after the disuse of antibiotics, once a resistant pool of micro-organism has been established. However, it is not clear whether the same conclusions can be reached if there is a fitness cost for maintaining resistance. Another recent method for combating infections is to disrupt the quorum sensing mechanism of pathogens, which is commonly used by pathogens for disease progression [22]. This disruption is known as quorum quenching [32, 33]. Beckmann's team [34] uses DOs to examine whether pathogens can be resistant to quorum quenching. Their results [34] suggest emerging resistance to quorum quenching by evolving to require fewer pathogenic organisms required to reach a quorum. This is supported by Czaran and Hoekstra [35], who analyzed the same phenomenon using DOs.

4. Genetic Adaptability

Adaptation is one of central tenets of evolutionary theory where evolved populations can be explained as adaptation [36]. This can be seen as improved fitness after the adaptation process. Wagernaar and Adami [36] suggest that DO are able to adapt to new environments after they are well adapted to other environments even though the new environments are orthogonal to their previous environments in term of rewarded behavior, which has been shown in bacterial evolution. Moreover, Yao et al. [37] suggest a possibility that unused beneficial traits in previous environments may be inactivated in the new environments. These suggest that DOs may be a suitable platform for adaptability studies. However, one of the main questions arises from the observation of abundance deleterious mutations compared to neutral or slightly beneficial mutations [38, 39]. Using DOs, McFadden and Knowles [40] find that deleterious mutations caused by transposons have a role to play in overcoming evolutionary stagnation. This is supported by Covert III [41] showing that deleterious mutations may be stepping stones to facilitate adaptive evolution, which is similar to a “one step backwards two step forward” approach, and the overall evolution proceeds with a faster rate compared to one with no deleterious mutations. This suggests that biologically observed deleterious mutations at this point of time may be evolutionary local minima towards better fitness. However, this points to a new question – how are organisms able to handle the effects of widespread, though temporary, deleterious mutations?

A logical way is by compensatory mutations to correct deleterious mutations. However, Edlund and Adami [42] suggest that evolutionary robustness in DOs may be increased by decoupling sections of the genome in a high mutation rate environment until sections of genomes are independent. This may suggest that genetic redundancy may be important for overall robustness so that a single deleterious mutation does not result in genetic collapse. This is supported by Gerlee et al. [43] examining pathway duplication using DOs and comparing DO results to yeast and suggest that duplication of functional pathways for redundancy may be an important evolutionary strategy. However, Frenoy et al. [44] present a case whereby entangled genome architecture may promote cooperative traits and robustness against mutations, which is contradictory to genome decoupling and segmentation presented by Edlund and Adami [42]. This underpins that complexity of evolution whereby opposing strategies may give rise to the same effect.

Wilke et al. [45] show that a flatter and lower fitness peak may be more evolutionarily stable than a higher but narrower fitness peak using DO, and term this as “survival of the flattest”. This phenomenon has been shown in further simulations using DOs and experimental study using plant pathogens [46]. This is also supported by Handel and Rozen [47] showing that the fitness landscape has many local minima and a trade-off, which is dependent on population size, between rate of adaptation and final fitness. The study by Wilke et al. [45] is on high mutation rate. This is consistent with Elena et al. [48] suggesting that mutation rate is proportional to robustness as a high mutation rate is likely to reduce the timespan where deleterious mutation will have an impact. However, Elena et al. [48] also suggest that population size is inversely proportional to robustness, which is partly resulting from the negative relationship between fitness and robustness. These works seem to suggest that high mutation rates are favoured. Hence, it may suggest that mutation rates may be optimized for long-term adaptation. However, Clune et al. [49] suggest that natural selection for optimized mutation rate is unlikely in a rugged fitness landscape. de Boer and Hogeweg [50] also suggest that moderate mutation rates leads to emergence of new phenotypes while higher mutation rates reduced diversity. These are consistent with Elena and Sanjuan [51] suggesting a complex interplay between genetic robustness, mutation rate, and the environment. This suggests that there may be different adaptation dynamics for smooth fitness landscape versus rugged fitness landscape.

Besides “survival of the flattest”, another school suggests that a different world can emerge from deferring selective pressure. Archetti [52] shows that low selective pressure can give rise to steep fitness gains and term this as “survival of the steepest”. This may in turn confer a first-arrival advantage to the organism [53]. This may suggest that the environment may play a crucial role in varying selective pressures where a harsh environment may exert a strong selective pressure which favour the “flattest” while a gentler environment may favour the “steepest” [54].

Collectively, these suggest that genetic adaptability is a complex interaction between the genetic history of the organism, the current state of evolution, and the environment. Of which, I am inclined to take the stand that the effects of the environment may play a major role as the main purpose of adaptation is for the organism to adapt to the environment. From this point of view, the above reviewed studies suggest that evolution may not have a preferred strategy but just require an appropriate strategy for adaptation. However, it will be interesting for future studies to examine situations and environments whereby a preferred strategy emerges and whether the organism can and will change an adaptation strategy based on the specific condition on hand.

5. Limitations of Digital Organisms in the Study of Genetic Evolution

Beside experimental practicality, a key advantage of DOs is the ability to study evolutionary processes, especially those pertaining to extinction events, which are unethical if not impossible to test. Such experiments can only be carried out virtually and relatively cheaply compared to experimental work. However, the key disadvantage of using DOs as a computer-based experimental platform lies in its applicability – how much of DO results are applicable to biological evolution and what are the limitations of such simulations? A limitation of evolutionary study is best said by Hugo DeVries – *"Natural selection may explain the survival of the fittest, but it cannot explain the arrival of the fittest"* [55]. Day [56] presents this by asking whether DOs can tell us the *likelihood that a pandemic with the 1918 Spanish influenza strain will ever occur again?* He suggests that DOs is only fully applicable if evolution is a closed process, that is, a finite set of outcomes. This suggests that DOs may be useful as a tool to test hypotheses with regards to evolution rather than a tool to observe evolution as it happens. Nevertheless, Stephen Gould [10] did argued that the outcome of life, both general and in detail will be very different from what we have today should evolution be repeated again. This points to a potential danger of using DOs as an open-ended tool to examine evolutionary process as each run may result in a different outcome. Hence, DOs may be best used as a tool to test specific evolutionary hypotheses using a closed view of evolution rather than a tool to examine evolutionary processes which is an open-ended view of evolution.

6. Conclusion

Digital organisms have provided a means to examine evolutionary hypotheses and events, such as extinction processes, which are practically impossible to examine in an experimental setting. The article reviews a number of such examinations in the area of emergence of specialized cells, chemical and environmental resistance, and genetic adaptability. Although such studies have provided insights into specific evolutionary hypotheses, it is unlikely that digital organisms are suitable to observe evolutionary process unbounded by specific hypotheses.

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