Modeling Epigenetic Evolution in a Fluctuating Environment

Trygve Bakken[1], Kiki Benzon[2], Li Xin[3], Mu Yifen[4], Ruan Xiao[5], Xia Xi[4], and Zhai Jixian[6]

[1]University of California, San Diego, USA, [2]University of Lethbridge, Canada, [3]Tsinghua University, China, [4]Academy of Mathematics and Systems Science, Chinese Academy of Sciences, [5]Peking University, China, [6]Institute of Genetics and Developmental Biology, Chinese Academy of Sciences.

## Summary

Epigenetics—heritable changes outside the genome—can provide organisms with a mechanism for phenotypic evolution in response to a variable environment. Here, we examine whether the average fitness of a population can be increased if individuals "anticipate" an environmental shift during reproduction via an epigenetic mechanism. We find that in both finite and infinite populations, there is an optimal fraction of offspring with a phenotype different from that of their parents that maximizes a population's fitness.

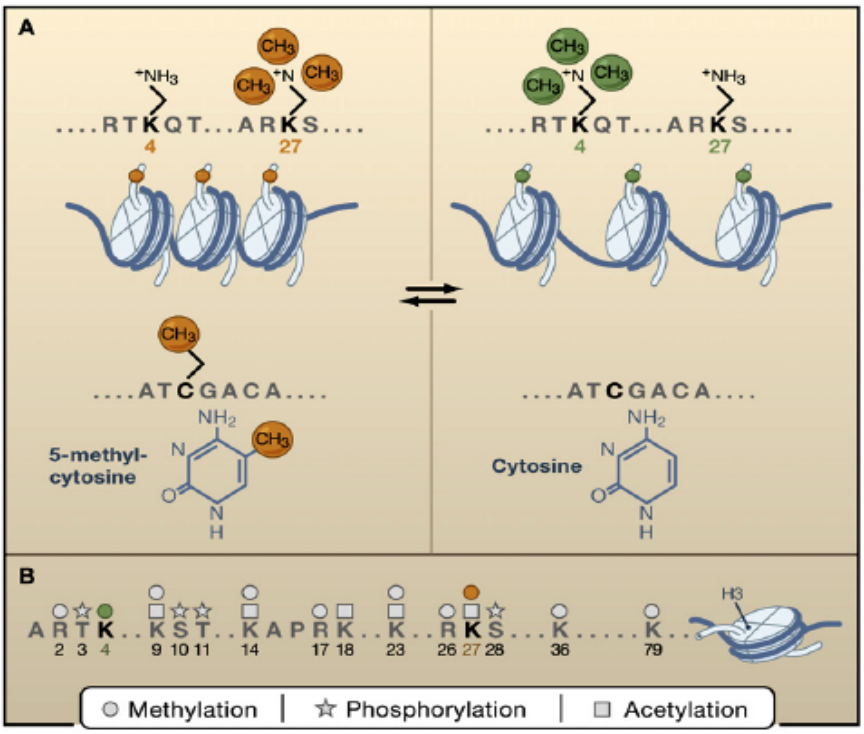
## Introduction

Epigenetics is a growing field of inquiry that is concerned with the principles, mechanisms and effects of non-genetic inheritance. In a special issue of *Cell* devoted to epigenetics, Goldberg *et al.* define the field as "the study of any potentially heritable change in gene expression or cellular phenotype that occurs without changes in Watson-Crick base-pairing of DNA".[1] Now a discrete branch of evolutionary biology, epigenetics emerged from a loose constellation of studies on various organisms that demonstrate a capacity to pass along to their offspring a phenotypic modification that is not the product of gene mutation. Examples of this capacity include: position-effect variegation in the fruit fly *Drosophila*, paramutation in maize, silent mating type in the budding yeast *Saccharomyces cerevisiae*, X-chromosome inactivation in female mammals, imprinting, and RNA interference in heterochromatin formation in the fission of yeast *S. pombe*. Collectively, these examples suggest that selection and variability are less independent than once thought and may, in fact, be causally linked to both endogenous and exogenous environmental pressures. Phenotypic evolvability—governed by epigenetic processes—improves an organism's ability to cope with changing conditions.

The term "epigenetics" was introduced fifty years ago by Conrad Hal Waddington, who referred to phenotypic changes occurring from cell to cell during development as the "epigenetic landscape".[2] Recent studies have sought to reveal the molecular constituents of this landscape, towards determining how heritable phenotypic change may occur without gene mutation. In the first comprehensive volume on the subject, *Epigenetics* (2007), Allis *et al.* characterize these changes as "the sum of the alterations to the chromatin template that collectively establish and propagate different patterns of gene expression (transcription) and silencing from the same genome".[3] Alterations to the chromatin template are most commonly produced by tagging small molecules to DNA and histones [see Fig.1] and by RNA interference. While research has confirmed that these mechanisms are involved in epigenetic processes, there are doubtless other contributing elements that remain to be identified. In addition to

itemizing the epigenetic arsenal, further research will have to determine how these changes propagate to daughter cells during mitosis. Still another site of investigation is the role of epigenetic phenomena in evolution and population dynamics. Recent work by Rando *et al*. indicates that epigenetic mechanisms have evolved, at least in part, to influence the timing and genomic location of heritable variability; Rando and his colleagues maintain that "organisms that have developed methods to protect vital phenotypes for which abrupt changes in selection are unlikely while maximizing variability for phenotypes that have to respond to frequent variations in selective pressure may have had a selective advantage over individuals that did not have such systems"[4]

Figure 1. Epigenetic Mechanisms: Methylation, Phosphorylation and Acetylation (Bernstein *et al.*, *Cell*,




2007). (A) illustrates the structure and effects of cytosine methylation (repressive/red) and two histone marks: H3K27 methylation (repressive/red) and H3K4 methylation (activating/green). (B) illustrates the diversity of histone H3 modifications.

The current study seeks to quantify this "selective advantage." To what extent, we ask, do epigenetic systems of inheritance improve the relative fitness of a population in a variable environment? Is there an optimal proportion of offspring with a capacity for epigenetic inheritance, such that the fitness payoff outweighs the cost of producing offspring that may not thrive in current environmental conditions? While devising a method to tackle these questions, it occurred to us that an epigenetic system of inheritance, with its many dynamic variables and periodicities, is a type of complex adaptive system—what John Holland has dubbed "cas"—a network with many different levels of organization, where agents work in parallel and control is highly dispersed.[5] Complex adaptive systems continually revise and rearrange their constituents in response to conditions both within and without the system itself. Likewise, in epigenetic systems, progressive changes in gene expression occur in response to intra- and extra-cellular environments. The concepts

and modeling tools used to interpret complex adaptive systems allow us to better understand the function and effects of epigenetic phenomena in relation to larger evolutionary processes.

## Methods

We posited two phenotypes (*A* and *B*) and two environments ($E_a$ and $E_b$) cycling periodically. Phenotype *A* has greater fitness in environment $E_a$, while phenotype *B* has greater fitness in environment $E_b$. One phenotype *A* individual is hemizygous with the A allele, and the other is heterozygous at the same locus with A and B alleles. However, the B allele is epigenetically silenced, and so both individuals have the same phenotype *A*. [see Fig. 2]

In our model we gave a slightly reduced fitness to $AB^S$ versus A, in order to account for the cost of maintaining this epigenetic silencing. $AB^S$ individuals can have offspring with either A or B allele silenced, i.e. $A^SB$ or $AB^S$ in a proportion *n*. Since silencing A or B also changes the phenotype to B or A, this mechanism can have a profound impact on the offspring's fitness. For example, if an $AB^S$ individual (*A* phenotype) has an $A^SB$ offspring (*B* phenotype), the offspring will have increased fitness as a result of this shift in silencing as long as the environment is $E_b$. The net population fitness in any generation is dependent on the number of individuals with phenotypes *A* and *B*, and this in turn is dependent on the proportion *n* of offspring that have a different allele silenced than their parent.

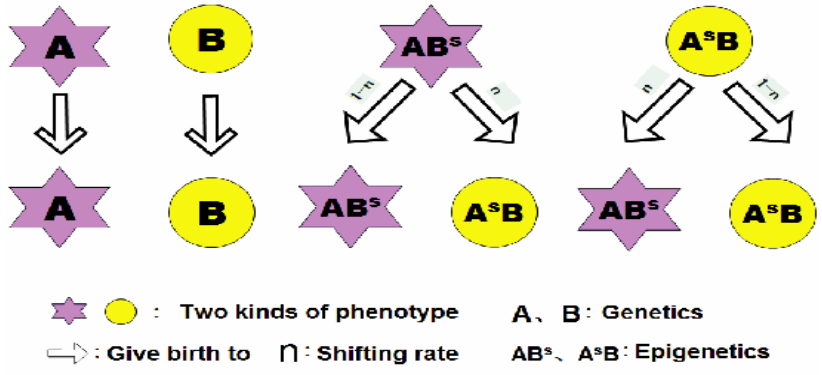



Figure 2. Genetic and Epigenetic Patterns of Inheritance for Phenotypes *A* and *B*.

We wanted to explore how population fitness changed when we varied *n* and the periodicity of environmental shifts. First we constructed a mathematical model that allowed us to analyze a continuous range of parameters and produce a fitness landscape for the total population. Next, we programmed an agent based model that allowed us to explore the fitness effects of a finite population and resources, and non-periodic environmental changes.

## Mathematical Model

In order to ascertain how different evolutionary mechanisms affect population fitness in a fluctuating environment, we devised a mathematical model that would reflect the fitness

landscape for the total population within a continuous range of parameters. In this instance, we considered the evolutionary dynamics of a population with infinite resources. We assumed a negligible mutation rate, and so epigenetic not genetic shifts in phenotype were possible. As stated above, we posited four "epi-genotypes" ($AB^S$, $A^SB$, A, and B) and set three parameters:

| | |
|---|---|
| $s$ | fitness cost due to epigenetic mechanism |
| $n$ | proportion offspring that switch epi-genotypes (and therefore phenotypes) |
| $\tau$ | number of generations in each environmental epoch |

We produced three matrices, where

| | |
|---|---|
| $M$ | epigenetic mutation rate |
| $W_A$, $W_B$ | fitness in environments $A$ and $B$, |
| $MW_A$, $MW_B$ | transition matrices from one generation to the next: |

$$M = \begin{array}{c} \begin{matrix} A & AB^S & A^SB & B \end{matrix} \\ \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1-n & n & 0 \\ 0 & n & 1-n & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \end{array} \qquad W_A = \begin{pmatrix} 1+s & 0 & 0 & 0 \\ 0 & 1+s & 0 & 0 \\ 0 & 0 & 1-s & 0 \\ 0 & 0 & 0 & 1-s \end{pmatrix} \qquad W_B = \begin{pmatrix} 1-s & 0 & 0 & 0 \\ 0 & 1-s & 0 & 0 \\ 0 & 0 & 1+s & 0 \\ 0 & 0 & 0 & 1+s \end{pmatrix}$$

We calculated $X(2\tau)$, the vector of frequencies of different epi-genotypes after one cycle between environments $E_a$ and $E_b$. $w$ bar normalizes $X(2\tau)$ so that all $x_i$ values are still frequencies.

$$X(2\tau) = \frac{1}{\overline{w}}(MW_A)^\tau (MW_B)^\tau X(0) \qquad \overline{w} = \sum_{i=1}^{4} [(MW_A)^\tau (MW_B)^\tau X(0)]_i$$

We calculated the maximum eigenvalue of vector $X(2\tau)$, which gave us the maximal fitness of that population after it had reached equilibrium. We repeated this for a range of $\tau$ and $n$ and plotted the fitness landscape of the population [see Fig. 3], which has several interesting features.

We noted that for even $\tau$ and more stable environments ($\tau > 7$), it is optimal if some offspring are different than their parent. The parents are in effect gambling that even though the environment has been stable for many generations, there is a chance that it will shift in the next generation, and so they pass on a different phenotype. In fact, $n = 0.005$ for $\tau = 1000$, so even in very stable environments, organisms with an epigenetic mechanism are more fit than those with none.

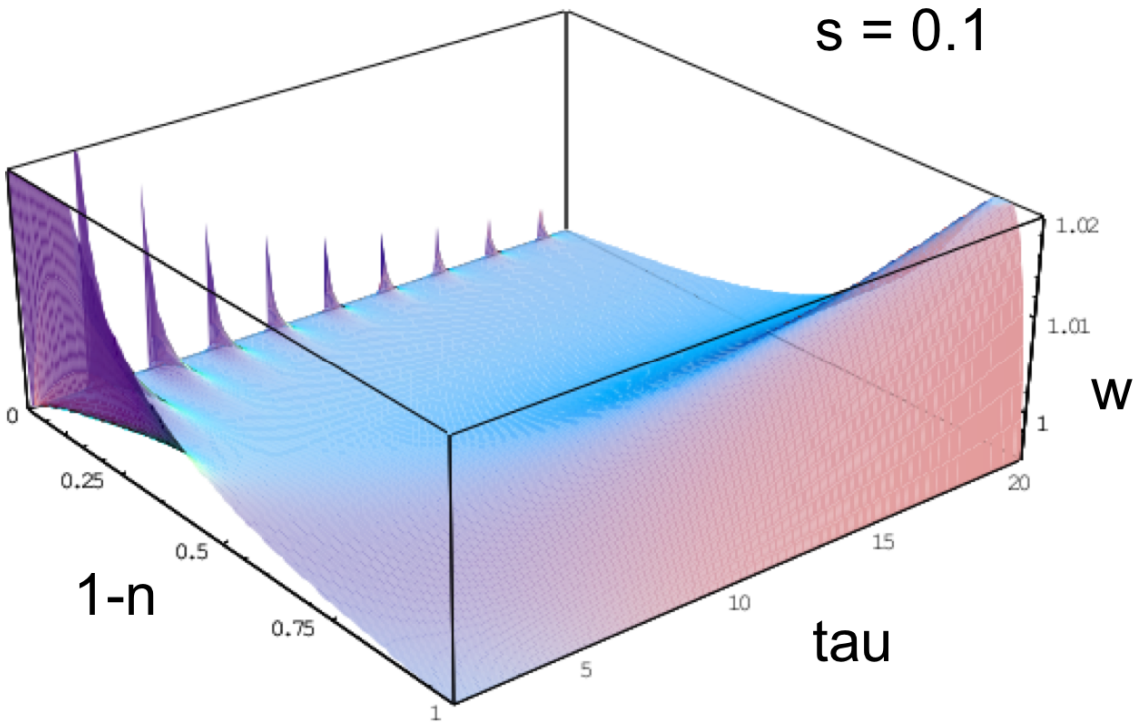



Figure 3. Fitness Landscape.

More striking are the peaks in *w* during shorter epochs (smaller τ). In order to examine this more closely, we plotted values of *n* that maximize fitness for each τ in the landscape [see Fig. 4]. We found that $n = 1$ (all offspring have a different epi-genotype from their parent) is optimal for odd $\tau < 8$. This is obvious for the case of $\tau = 1$ because the environment shifts every generation, and so it is beneficial to switch phenotypes. This trend does not hold true for $\tau > 8$ because it is detrimental to "anticipate" an environmental shift that occurs so many generations in the future.

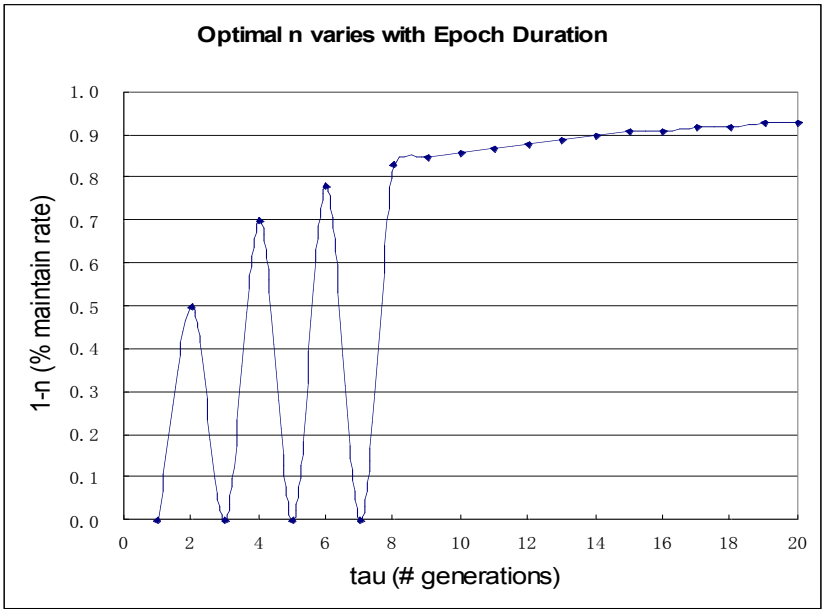



Figure 4. Optimal *n* in Variable Epoch Duration.

**Agent Based Model**

In addition to providing a point of comparison with our mathematical results, the agent based model allowed us to simulate a more realistic situation, where population and resources are finite, and environmental fluctuations are not strictly periodic. In our first set of agent based trials (Case 1), we wanted to determine which inheritance mechanism—epigenetic or genetic—would generate a more competitive population in a fluctuating environment. We again posited four epi-genotypes: $A$, $AB^s$, $A^sB$, and $B$ . Using NetLogo, we processed these types through both cycling and randomly fluctuating environments [Figs. 5 and 6, respectively]. The resulting outcomes were commensurate with those of the matrix model.

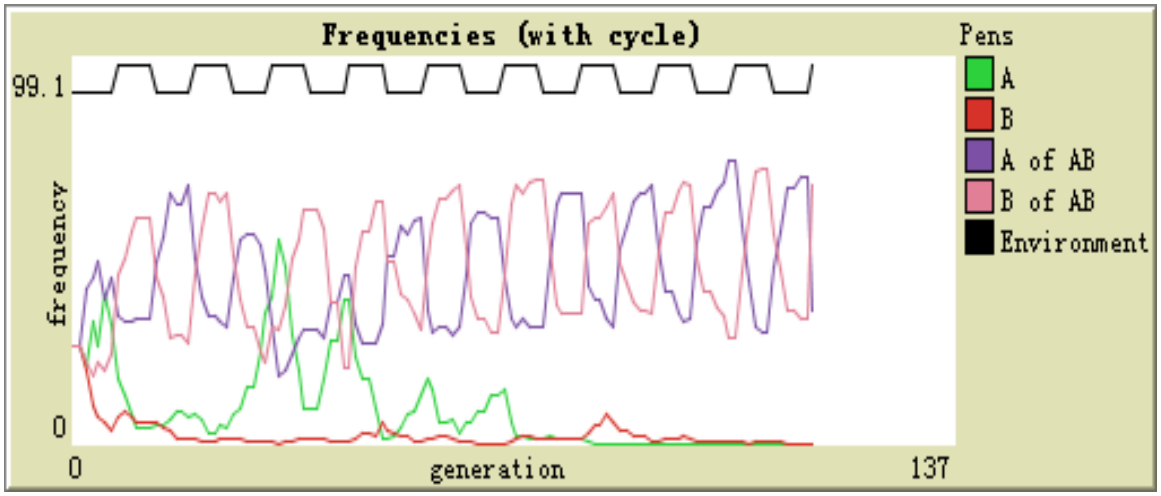



Figure 5. Cycling Environment.

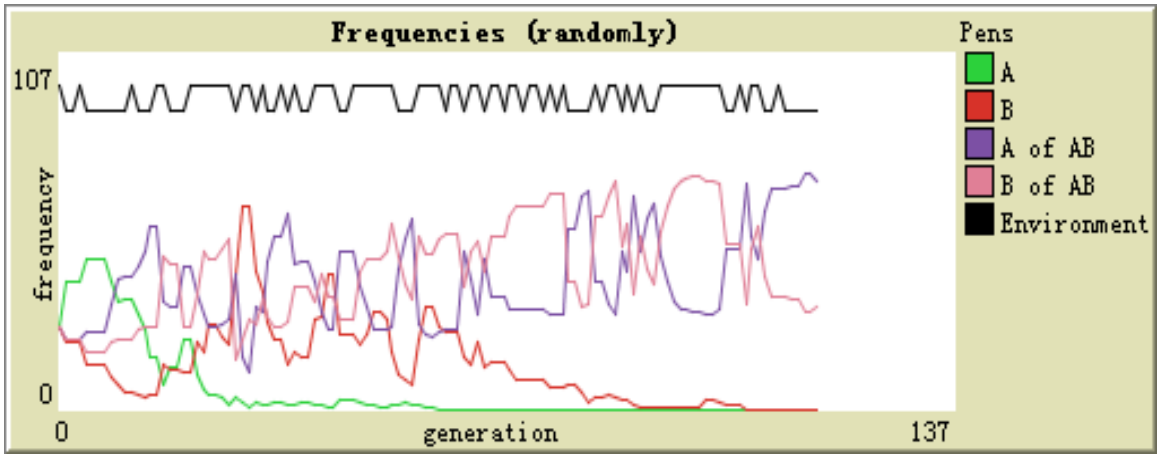



Figure 6. Randomly Fluctuating Environment.

The black curve at the top of each chart denotes environmental changes between conditions that favor phenotype $A$ and those that favor phenotype $B$. In both cycling and random environments, frequencies of $A$, $AB^s$, $A^sB$, and $B$ change in relation to

environmental fluctuation. After many generations and for many shifting rates ($n$) and fitness ranges ($1 \pm s$), $f(A$ and $B) \rightarrow 0$, leaving only organisms with a capacity for epigenetic inheritance. In a stable environment ($\tau >> 1$), $f$(A or B) = 1. As shown in the matrix model, the agent based model indicates that there is an evolutionary advantage to having an epigenetic mechanism despite the cost of producing offspring that are unfit for current environment.

In a second set of agent based trials (Case 2), we wanted to determine the optimal shifting rate of $n$ ("opt-$n$") in environments with different periodicities. We posited epi-genotypes $AB^{n1}$, $AB^{n2}$, etc., with different $n$. As in Case 1, the agent based model in Case 2 reproduced the optimal $n$ that was calculated from the fitness landscape. [Fig. 7] When the matrix model predicted 2 values of $n$ that produced a high fitness for a given $\tau$, both epi-genotypes dominated the population in repeated agent based modeling trials.

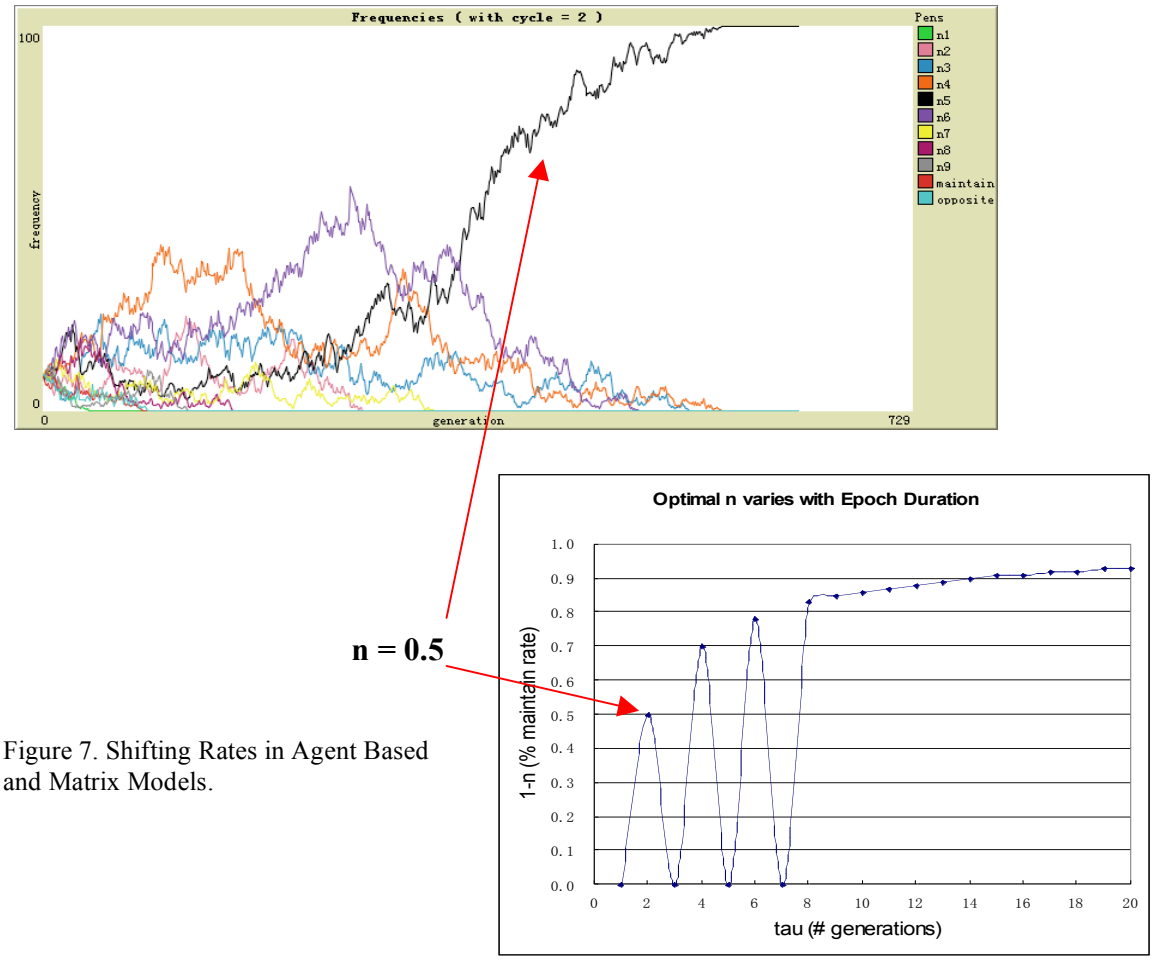



Figure 7. Shifting Rates in Agent Based and Matrix Models.

Our final task was to determine how the system would behave in a fluctuating but aperiodic environment. Our model indicates that, in a random environment, $f(AB^s$ and $A^sB)$ would usually approach 1, but the system is more sensitive to the value of $n$. Thus, we confimed that optimal $n$ depends upon the particular sequence of environmental changes. As Figure 8 illustrates, $n6$ ($n$ = 0.6) prevails (where E-S is 1001100010001101000011101 0…).

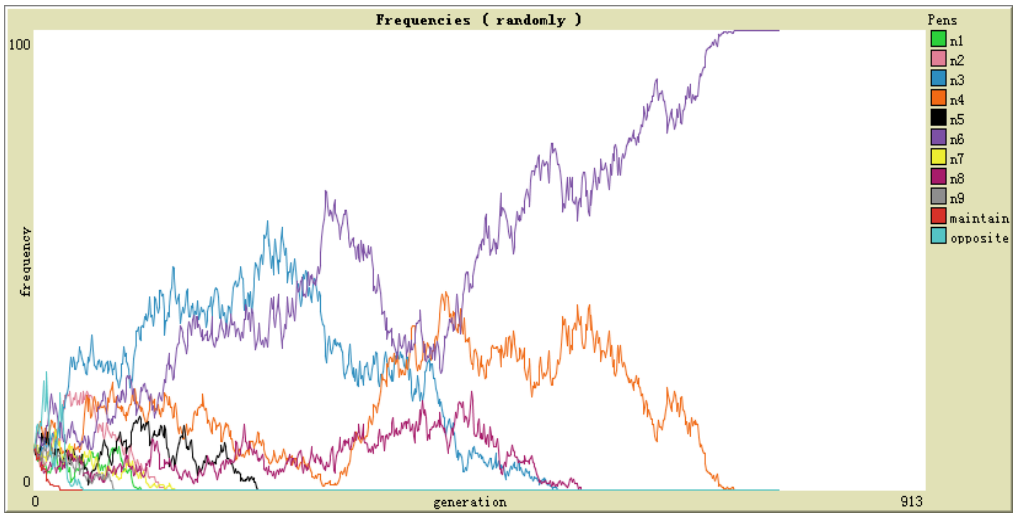



Figure 8. The frequencies of species *AB* with different S-R *n* change under randomly oscillating environment. finally

## Discussion

Recent studies in evolution have revealed that variation and inheritance are not exclusively contingent on random gene mutation. Indeed, rates of mutation themselves can evolve: in their article "Evolution of Genetic Potential," Meyers and Lachmann refer to the regulation of evolution as "genetic potential"—that is, an "enhanced potential for mutations to give rise to novel (beneficial) phenotypes".[6] Meyers and Lachmann find that genetic potential is most profound during periods of rapid environmental fluctuation, when organisms benefits from the greater phenotypic range that a heightened sensitivity to mutation can generate. Environmental conditions, moreover, have proven to govern the expression or repression of specific heritable traits, without the requirement of genomic mutation. Organisms that are able to respond to or anticipate environmental changes through an epigenetic mechanisms display a greater robustness over time. Whether such mechanisms support a Lamarckian evolutionary view is disputable, but

## Conclusion

In this study, we used evolutionary modeling for complex adaptive systems to understand the effects of epigenetic inheritance upon population dynamics and fitness. We found that epigenetically governed shifting between phenotypes has a significant advantage in a fluctuating environment, compared to genetic mutation alone. In a simple model of both infinite and finite populations, there is often a strong evolutionary advantage for individuals with an epigenetic mechanism that allows for phenotypic selection in offspring. This is true even though phenotype inheritance is a fixed proportion *n*. This is often true even in unpredictable environments.

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**References**

Allis, C. David. Thomas J. Jenuwein, Danny Reinberg. *Epigenetics*. Associate Ed. Marie-Laure Caparros. (2007) Cold Spring Harbour, NY: Cold Spring Harbour Laboratory Press.

Goldberg. Aaron. C. David Allis and Emily Bernstein. (2007) "Epigenetics: A Landscape takes shape." *Cell* 128: 637 – 644.

Holland, John. *Adaptation in Natural and Artificial Systems*. (1992) Boston: MIT Press.

Meyers LA, Ancel FD, Lachmann M (2005) "Evolution of Genetic Potential." *PLoS Comp Biol* 1(3): e32.

Minc, Leah D. (1986/03)."Scarcity and survival: The role of oral tradition in mediating subsistence crises." *Journal of Anthropological Archaeology* 5(1): 39-113.

Rando, Oliver J. and Kevin J. Vertrepen. (2007) "Timescales of genetic and epigenetic Inheritence" *Cell* 128: 665 – 668.

Waddington, C.H. (1957) *The Strategy Of The Genes*. George Allen & Unwin, London.

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[1] Goldberg et al., 637.
[2] Waddington, 11-58.
[3] Allis *et al.*, 29.
[4] Rando *et al*. The researchers find that epigenetic mechanisms such as hypervariable contingency loci and error-prone DNA replicases "seem to tune the variability of a given phenotype to match the variability of the acting selective pressure" (666)
[5] Holland, 1992.
[6] Meyers and Lachmann, 0239.