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Evolutionary dynamics of redundant regulatory control

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ABSTRACT

Many complex regulatory processes concern tracking a constant or variable set point. Examples include temperature homeostasis, rhythmic oscillation, and the concentration of key metabolites and enzymes. Control over homeostatic or tracking phenotypes often depends on multiple, overlapping regulatory systems. In this paper, I develop a theory for the evolutionary dynamics of redundant regulatory control architecture. Prior theories analyzed the evolution of redundant control architectures by the balance between improved performance for additional redundant control weighed against the decay by germline mutation that arises in characters with overlapping function. By contrast, I argue that germline mutation is likely to be a very weak balancing force in evolutionary dynamics. Instead, I analyze the evolutionary dynamics of redundant control by a balance between the benefits of reduced tracking error and the costs of building and running the multiple control systems. In one particular mathematical model that highlights key features of evolutionary dynamics, additional redundant control reduces tracking error multiplicatively but contributes to costs additively. In that model, the performance landscape has multiple peaks of the same height, one peak for each level of redundancy and the associated optimal investment per control structure. The multipeak landscape imposes evolutionary stasis, in which control systems resist invasion by increased or decreased levels of redundancy. However, fluctuating environments likely favor a rise in redundancy over time. With greater redundancy, investment per individual control structure declines, causing a decay in the performance of each individual dimension of control. I conclude that the costs of control structures may influence regulatory architecture.

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1. Introduction

In this paper, I develop a mathematical model to study the evolutionary dynamics of redundancy. I have in mind complex regulatory control problems, such as temperature or blood pressure homeostasis, rhythmic oscillation, osmotic balance, nutrient acquisition, and reaction rates to maintain proper concentrations of key molecules. All of these regulatory problems concern tracking a constant or variable set point. So, we can describe performance in terms of minimizing the tracking error and in terms of the costs required to build and run the multiple component systems that affect tracking error.

I focus on an abstract model, because I want to understand the fundamental dynamical properties common to all cases by which organisms may acquire or lose costly redundant components that contribute to performance. Certainly, each distinct biological problem will differ in crucial ways that we must ultimately

understand. But to grasp the key differences, we must first understand the shared aspects of evolutionary dynamics set by the structure of the problem.

My main contribution is to develop an economic perspective to analyze architectural aspects of regulatory control. I introduced my economic approach in a prior paper (Frank, 2007), in which I analyzed the evolutionary dynamics of characters that influence robustness with regard to both the costs of building and maintaining protective characters and the benefits of protection against perturbations. In this paper, I turn to the evolutionary dynamics of redundancy as influenced by the costs of additional component systems and the benefits that additional components contribute to performance.

Prior empirical or theoretical work has rarely considered the costs of multiple regulatory controls over a single aspect of performance. Instead, such work typically focuses solely on the benefits of enhanced performance, or the balance between enhanced performance and the decay by mutation that arises when multiple control systems have overlapping function. By contrast, I argue that costs play an essential role in shaping the architecture of regulatory control systems.

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2. Background

To set the background, I first place my study in the context of the different kinds of redundancy. I then discuss different lines of thought on how evolutionary forces shape redundant control.

One must distinguish two types of redundancy. Protective redundancy means that multiple structures or mechanisms serve the same functional purpose, and each can act alone in achieving full performance. Protective redundancy serves as a safety factor, maintaining full performance after failure of some of the redundant components.

By contrast, performance redundancy means the presence of multiple component systems that contribute to the same function. Redundant components may act together such that performance depends on the number of components present. In that case, failure of one component causes a degradation in performance—the remaining systems provide only partial protective redundancy.

Some authors prefer other terms to describe performance redundancy, because the component systems may differ functionally, structurally, or mechanistically (Edelman and Gally, 2001). However, no generally accepted taxonomy exists. Indeed, precise definition can be difficult, because components may initially be duplicated and then subsequently diverge structurally or functionally (Brookfield, 1992; Wagner, 1994). In addition, empirical studies often resolve poorly between complete and partial overlap of function.

Much prior work has focused on protective redundancy, in which loss of a component has little or no effect on performance so long as other fully functional components remain. In those studies, evolutionary dynamics usually depend on the balance between the benefits of protection against component failure weighed against degradation caused by mutation (Orr, 1995; Nowak et al., 1997; Wagner, 1999).

Some work has emphasized performance redundancy, in which multiple components combine to improve function. Those studies emphasize the benefits of multiple component systems to stabilize or enhance function. But those studies either leave open the problem of what balancing force prevents ever increasing redundancy to improve performance, or the studies balance improvements from redundancy against mutational decay (Brookfield, 1992; Tautz, 1992, Krakauer and Nowak, 1999; Nunney, 2003; Frank, 2003, 2004).

By contrast, I focus on an economic perspective that balances the benefits of multiple component systems against the costs of building and running component processes. Few studies have analyzed redundancy and regulatory control from the economic perspective of costs and benefits. A research lineage from the biomechanical and physiological disciplines focuses on the balance of costs and benefits in evolutionary design (Alexander, 1981; Taylor and Weibel, 1981; Weibel et al., 1998; Diamond, 2002). That work often emphasizes safety factors, in which excess capacity functions to protect against relatively rare but potentially severe challenges. In that regard, the safety factors act much like redundancy in many genetic theories, in which redundant components protect against relatively rare but potentially devastating failures in individual components. However, the work on safety factors in biomechanics and physiology did not address redundancy or regulatory control.

Wagner (2005a, 2007) estimated that, in microbes, even small increases in gene expression impose significant performance costs. These studies support my argument that, in the analysis of regulatory design, one must pay attention to the costs associated with regulatory control. However, Wagner did not specifically consider how the combination of costs and benefits influence economic aspects of regulatory design. Here, I develop

the economic perspective to analyze architectural aspects of regulatory control.

3. The model

Organismal performance depends on how closely an individual can track a set point and on the cost of control structures used in tracking. Organisms gain by reducing the tracking error and by reducing the costs of control structures. To develop a model, let the performance index be W , which depends on the tracking error, E , and the total costs, C . The tracking error can be converted into the same units as the costs by letting r be the exchange rate between tracking errors and costs, such that total performance is

$$W = -rE - C,$$

where terms are negative because tracking errors and costs reduce performance.

I focus on two control variables. First, each control system is regulated by a character, x . Second, an organism has n redundant control systems, each system with character x_i for $i = 1, \dots, n$. I express the character values in units of cost, such that the total cost over the n control systems is $C = \sum_{i=1}^n x_i$. We may interpret x as the fixed cost an organism invests in regulatory component i . The tracking error is a function of investment in the control characters, x_i , and the number of control structures, n , such that $E = f(\mathbf{x}, n)$, where \mathbf{x} is the n -dimensional vector of character values.

In the simplest case, all the control variables take on the same value, $x_i = x$, for all i . Then we can write performance as

$$W(x, n) = -rE - C = -rf(x, n) - nx. \quad (1)$$

4. Optimal control variables

For a fixed number of redundant control structures, n , performance is maximized at

$$\frac{dW}{dx} = -rf' - n = 0 \quad (2)$$

when the second derivative is less than zero

$$\frac{d^2W}{dx^2} = -rf'' < 0, \quad (3)$$

where primes denote differentiation with respect to x . Thus, if $f' < 0$ and $f'' > 0$, the value x_n^* maximizes W at $f'(x_n^*, n) = -n/r$, given a fixed value of n .

5. Conditions for increase or decrease in redundancy

In this section, I fix the control characters at their optimal value x_n^* for n redundant control systems. I then ask whether individuals who add or lose a single redundant control structure can gain in performance, thereby causing an evolutionary change in redundancy.

Consider first a reduction from n to $n - 1$ redundant control systems, holding constant the character value at x_n^* . An individual gains by losing a control system if $W(x_n^*, n - 1) - W(x_n^*, n) > 0$, which can be expanded as

$$\begin{aligned} W(x_n^*, n - 1) - W(x_n^*, n) &= -r\Delta E - \Delta C \\ &= -r[f(x_n^*, n - 1) - f(x_n^*, n)] + x_n^*. \end{aligned} \quad (4)$$

The condition for a reduction in redundancy to gain an initial advantage is $-\Delta C > r\Delta E$. Here, $-\Delta C$ is the gain achieved from

reduced costs, and $r\Delta E$ is the loss suffered from increased tracking error. In this case, reduced redundancy causes ΔC to be negative and ΔE to be positive.

Next, consider an increase from n to $n + 1$ redundant control systems, holding constant the character value at x_n^* . An individual gains by acquiring an additional control system if $W(x_n^*, n + 1) - W(x_n^*, n) > 0$, which can be expanded as

$$W(x_n^*, n + 1) - W(x_n^*, n) = -r\Delta E - \Delta C = -r[f(x_n^*, n + 1) - f(x_n^*, n)] - x_n^* \quad (5)$$

The condition for a reduction in redundancy to gain an initial advantage is $-r\Delta E > \Delta C$. Here, $-r\Delta E$ is the gain from reduced tracking error, and ΔC is the loss from the cost of the additional redundant control system. In this case, increased redundancy causes ΔC to be positive and ΔE to be negative.

The formulae in this section give the general conditions to determine if an initial increase or decrease in redundancy is favored, given a population currently fixed for n redundant control structures. The next section analyzes an exemplar of $f(x, n)$ in order to calculate which conditions are satisfied under particular assumptions.

6. Exponential benefits

Let $f(x, n) = e^{-xn}$. This assumption bounds the tracking error between zero and one, and the error decays exponentially with increased investment in control measured by x .

Note that, under this model, tracking errors combine multiplicatively, whereas costs accumulate additively. Multiplicative combination of tracking errors makes sense, because an additional control system necessarily reduces the existing error by some fractional amount: given a current error level, E , an additional fractional move the error toward zero to a new level E' , such that $0 \leq E' \leq E$. In this particular case, the fractional reduction in error is e^{-x} . By contrast with multiplicative reductions in error for each additional system, additive costs per system make sense, because each additional control system typically adds roughly the same burden as the prior system. Certainly, other assumptions are possible, but multiplicative combinations of tracking error reductions and additive costs present the simplest and most reasonable default case.

The optimal investment in control can be calculated from the condition given above: $f'(x_n^*, n) = -n/r$, yielding the optimum

$$x_n^* = \log(r)/n$$

for $r > 1$. At x_n^* , $f' < 0$ and $f'' > 0$, so this value of x_n^* is a local optimum, as described by Eq. (3). These conditions combined with Eq. (3) also justify the assumption that $x_i = x$ for all i . Later, we will need the tracking error given the optimum value for the control characters obtained in a population with n control structures, subsequently placed in an individual with m control structures, yielding

$$f(x_n^*, m) = e^{-x_n^*m} = r^{-m/n} \quad (6)$$

In a population fixed for n control structures at investment per control structure x_n^* , performance is

$$W(x_n^*, n) = -(1 + \log(r)).$$

Thus, performance in a fixed population at its optimum is independent of n . So, changes in n , followed ultimately by equilibration of x_n^* to a new value, have no effect on performance. However, this ultimate neutrality with regard to performance does not tell us how the evolutionary dynamics will play out, because, in a fixed population, an initial increase or decrease in n may be favored.

Eq. (4) gives the condition for an initial rise in frequency of individuals with reduced redundancy from n to $n - 1$, holding constant x_n^* . Reduced redundancy cannot invade if $-r[f(x_n^*, n - 1) - f(x_n^*, n)] + x_n^* < 0$. Using Eq. (6) and expanding yields the condition to prevent invasion by reduced redundancy as

$$r^{1/n} > 1 + \log(r)/n$$

for $r > 1$. This condition is always satisfied because the two sides are equal at $r = 1$, and, by differentiation, one can show that the left side increases faster than the right side as r rises from one. Thus, if we hold x_n^* constant, reduced redundancy cannot invade.

Eq. (5) gives the condition for an initial rise in increased redundancy from n to $n + 1$, holding constant x_n^* . Increased redundancy cannot invade if $-r[f(x_n^*, n + 1) - f(x_n^*, n)] - x_n^* < 0$. Using Eq. (6) and expanding yields the condition to prevent invasion by increased redundancy as

$$1 - r^{-1/n} < \log(r)/n$$

for $r > 1$. This condition is always satisfied because the two sides are equal at $r = 1$, and, by differentiation, one can show that the right side increases faster than the left side as r rises from one. Thus, if we hold x_n^* constant, increased redundancy cannot invade.

In this analysis, I have held x_n^* constant and analyzed only how changes in n affect evolutionary dynamics. However, we can make a much stronger statement. Because $W(x_n^*, n)$ is independent of n , simultaneous changes in x and n cannot invade a fixed population with n redundant control structures and investment per structure of x_n^* . In particular, $W(x_n^*, n) = W(x_m^*, m)$; and $W(x_n^*, n) > W(y, n)$ for $y \neq x_n^*$; and $W(x_n^*, n) > W(x_n^*, m)$ for $m \neq n$; thus, $W(x_n^*, n) > W(y, m)$ for $y \neq x_n^*$.

Fig. 1 shows graphically why evolutionary stasis tends to be favored, such that a population currently fixed at n redundant control systems resists invasion by individuals with greater or fewer redundant systems. Each performance peak has the same height for the different values of (x_n^*, n) for various levels of redundancy, n . Performance is lower for any combination of (x, n) not on one of those peaks. Thus, evolutionary change must arise by peak shifts that cross valleys of lower performance.

7. Response to changed environment

In a static environment, the current level of redundancy resists invasion by individuals with additional redundancy and by

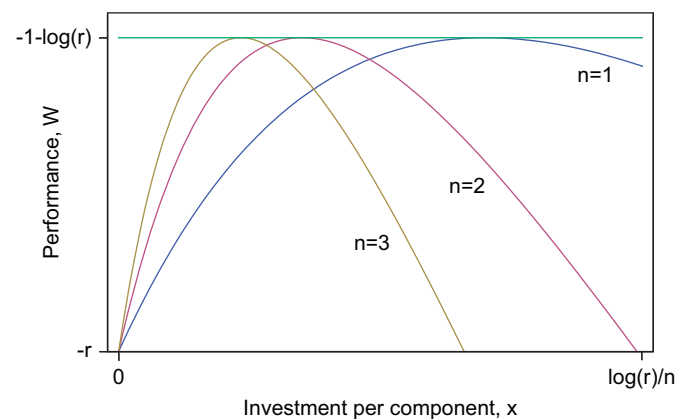


Fig. 1. The performance landscape. Performance, W , is plotted for values of x , the investment per control structure, and n , the level of redundancy. The performance landscape has one peak for each value of n . The peaks are the same height for different n . Thus, the performance landscape has multiple peaks of the same height, each peak separated by a valley with lower performance.

individuals with reduced redundancy. In this section, I consider fluctuations in the environment by studying changes in r . This parameter describes the exchange rate between the cost of redundant structures and the benefits of reduced tracking errors. More challenging environments may tend to increase r by putting greater weight on ability to track the environment.

Suppose a population has, for an extended period, experienced a relatively constant environment associated with a constant value of r . During this period, the population has become fixed for n redundant control structures, with investment per structure of x_n^* . With no change in environment, evolutionary dynamics favors stasis at the current level of redundancy.

During a challenging period, r may increase by a factor of k to $\hat{r} = kr$. An individual carrying an additional redundant structure, for a total of $n + 1$, has an advantage over the typical individuals with n redundant structures if

$$W(x_n^*, n + 1 | \hat{r}) - W(x_n^*, n | \hat{r}) > 0. \quad (7)$$

Given the formulae above and $\hat{r} = kr$, this condition favoring enhanced redundancy is satisfied when

$$k > \frac{\log(r)}{n(1 - r^{-1/n})}. \quad (8)$$

Fig. 2a shows that relatively small increases in k favor enhanced redundancy when holding x_n^* constant.

Environments may typically have some approximate baseline interspersed with periods of heightened challenge. During increased periods of challenge, redundancy may rise. With the addition of a redundant structure via duplication, it may often be that the duplicate structures diverge and acquire different functions. This combination of duplication and divergence may impose an upward bias in the tendency of organisms to accumulate functionally redundant structures that diverge to achieve either different functions or to combine to improve the original function by variant mechanisms.

If exceptionally challenging periods occur more frequently than exceptionally benign periods, and divergence of structural duplicates occurs, then reductions in redundancy may be rare. However, to round out the theory, it is useful to look at the condition for reduction in structurally identical control systems.

Following the method above, if the environment becomes less challenging, causing a decrease in r by a factor k to $\hat{r} = kr$, then

reduced redundancy is favored when

$$k < \frac{\log(r)}{n(r^{1/n} - 1)}.$$

Fig. 2b shows that this condition is nearly symmetric to the condition for an increase in redundancy, although the condition for a decrease is often more stringent.

In this analysis of response to an environmental change, I have focused on changes in n holding constant x_n^* . I do this because duplication or loss of a redundant structure is likely to happen on a faster time scale than equivalently significant changes in the character x . As n evolves, x will subsequently adjust at a slower pace. It is, of course, possible that x would change at the same rate or a faster rate than n . Such rapid evolution of x would alter the dynamics, but on the whole, the main qualitative forces acting directly on redundancy in response to environmental change likely remain as described here.

8. Discussion

This paper focused on how functionally similar systems combine to influence performance. Performance may, for example, be measured by the ability of an organism to track a constant or variable set point. In my models, the number of functionally similar systems—the redundancy—maintained by natural selection arises from a balance between the costs of building and maintaining additional components weighed against the benefits of reduced tracking error for additional component systems. By contrast, prior theories of redundancy emphasized the evolutionary balance between the inherited mutational decay of components and the benefits of protection against somatic or germline knockout of components: a balance between mutation and selection (see Section 2).

The prior work on mutation-selection balance established an essential framework, but I believe that my cost-benefit view will ultimately provide more insight into the evolutionary dynamics of homeostatic systems. The reason is that construction and maintenance costs are likely to be much stronger forces than decay of components by germline mutation. In general, inherited mutation is a weak evolutionary force (Proulx and Phillips, 2005). Theories that depend on the benefits of a phenotype balanced against germline mutation rarely provide compelling explanations for the evolution of complex phenotypes, apart from the repair systems that themselves control the rate of mutational errors.

In this paper, I analyzed a model in which an additional component system contributed both costs and benefits to total performance. The costs had an additive effect on performance. The benefits reduced tracking error multiplicatively—for example, if each component halved the tracking error, then two identical components together would reduce the error to one quarter of the prior value. These assumptions of additive costs and multiplicative benefits seem to form the simplest and most natural model of homeostatic tracking performance. I therefore regard this model as the best way to obtain a touchstone for understanding evolutionary dynamics, against which one may compare the dynamics that follow from more complex and particular assumptions.

The first main result describes the landscape of performance as a function of the number of redundant control structures, n , and the investment in each control structure, x . For each n , there is an optimal investment per control structure, x_n^* . Interestingly, the total performance at the optimum is the same for all values of n (Fig. 1). Thus, the performance landscape has n peaks of identical height, each peak separated from the others by a valley of lower performance.

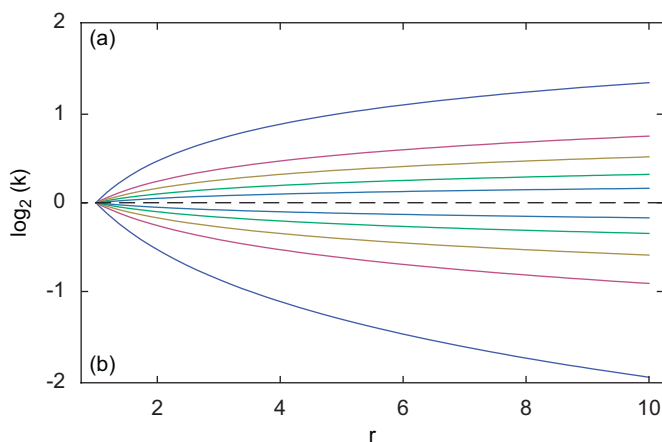


Fig. 2. Condition for change in redundancy as the environment changes. (a) Enhanced redundancy invades when $\log_2(k)$ is greater than the curves given for various values of n , which are, from top to midline: 1, 2, 3, 5, and 10. The condition for increase is given by Eq. (7). (b) Reduced redundancy invades when $\log_2(k)$ is less than the curves given for various values of n , which are, from bottom to midline, 1, 2, 3, 5, and 10. The condition for decrease is given by Eq. (8).

This multipeak landscape of performance imposes evolutionary stasis on the level of redundancy. At whatever level of redundancy, n , a population is currently fixed, natural selection disfavors both gains and losses in redundancy.

Although total performance remains the same at each peak, differences do arise in the performance contribution per component. As the number of redundant components increases, the investment per component declines in proportion to $1/n$. Thus, increased redundancy causes each individual component to decay in its ability, by itself, to control the tracking error. As redundancy increases, the system acquires a larger number of cheaper, lower performing components that together keep the total system at the same level of performance.

Certainly, additional nonlinearities likely occur in any real case, and those nonlinearities will affect the evolutionary dynamics and the changes in component parts. However, as redundancy increases, there will often be an overall tendency for components to become cheaper and, individually, to perform at a lower level. The aggregate performance may, however, rise, if, over some range of n , the combined benefits rise at a faster rate than the combined costs.

The second main result concerns the evolutionary response to temporary environmental perturbations. Returning to my touchstone model with simple multiplicative benefits and additive costs, evolutionary dynamics imposes stasis on n in a constant environment. Suppose, however, that during occasional periods, the environment becomes harsher. I modeled periodic environmental stress by altering the parameter r , which measures the exchange rate between the costs of investment in control structures and the benefits of reduced tracking error.

I first considered the population fixed at some level of redundancy, n , and the associated optimal allocation per control structure, x_n^* , given a constant, baseline value of r . I then raised r under the assumption that, during environmental stress, environmental tracking weighs more heavily on overall performance.

Increased environmental harshness, modeled by a small increase in r , favors duplication of an existing control structure, thereby increasing n , the level of redundancy (Fig. 2a). Similarly, exceptionally benign environments, modeled by reduced r , favor loss of an existing control structure, decreasing n (Fig. 2b). If the population becomes fixed at a different n , it remains at the new level of redundancy until further changes in r , because of the inherent stasis imposed by the multi-peaked performance landscape with valleys between the peaks.

There is, however, likely to be an upward bias favoring, over time, more rather than less redundancy. The upward bias may occur because of a slight asymmetry that requires a lesser magnitude of change toward harsh environments to favor increased redundancy when compared with the greater swing toward benign environments required to favor reduced redundancy (Fig. 2). In addition, environments probably impose more frequent periods of stress, with more rapid rates of onset, relative to less frequent periods of ease that may develop more slowly.

In summary, my model balanced the costs of multiple, redundant control systems against the benefits of reduced tracking error achieved with increased numbers of control systems. Under simple assumptions, with additive costs and multiplicative benefits, evolutionary dynamics imposes stasis on the level of redundancy. However, periods of environmental stress favor enhanced redundancy, whereas benign environments favor reduced redundancy. Asymmetries in the dynamics between harsh and benign periods, and a tendency for environmental harshness to be more common and more sudden, may create an

upward bias in the level of redundancy. Over the long term, increased redundancy is typically associated with little overall change in performance, because, with an increase in the number of control structures acting on the same tracking problem, the individual control structures tend to decay to cheaper, lower performance components.

Actual homeostatic systems may, over evolutionary time, improve in performance. The value of the present model is that such increased performance does not arise automatically by increased redundancy and complexity. Rather, there must be additional forces in play. For example, redundant control structures may arise by duplicating existing structures, as in the model here. However, after duplication, the control systems may then diverge to function in different and synergistically complementary ways (Brookfield, 1992; Wagner 1994, 1996, 2005b), improving overall performance without increasing cost. Once such synergistically beneficial systems arise, subsequent loss of a control system becomes unlikely. My model focuses on the evolutionary dynamics that influences the initial duplication. Subsequent synergistic divergence provides an additional process that influences the evolutionary dynamics of redundancy and complexity.

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