Journal of Developmental Origins of Health and Disease

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Original Article

Cite this article: Spencer HG, Pleasants AB, Gluckman PD, and Wake GC. (2022) A model of optimal timing for a predictive adaptive response. *Journal of Developmental Origins of Health and Disease* **13**: 101–107. doi: 10.1017/S2040174420001361

Received: 17 July 2020
Revised: 3 November 2020
Accepted: 8 December 2020
First published online: 13 January 2021

Keywords:
Developmental plasticity; evolutionary theory; mismatch; mathematical model

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A model of optimal timing for a predictive adaptive response

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Abstract

Predictive adaptive responses (PARs) are a form of developmental plasticity in which the developmental response to an environmental cue experienced early in life is delayed and yet, at the same time, the induced phenotype anticipates (i.e., is completely developed before) exposure to the eventual environmental state predicted by the cue, in which the phenotype is adaptive. We model this sequence of events to discover, under various assumptions concerning the cost of development, what lengths of delay, developmental time, and anticipation are optimal. We find that in many scenarios modeled, development of the induced phenotype should be completed at the exact same time that the environmental exposure relevant to the induced phenotype begins: that is, in contrast to our observed cases of PARs, there should be no anticipation. Moreover, unless slow development is costly, development should commence immediately after the cue: there should be no delay. Thus, PARs, which normally have non-zero delays and/or anticipation, are highly unusual. Importantly, the exceptions to these predictions of zero delays and anticipation occurred when developmental time was fixed and delaying development was increasingly costly. We suggest, therefore, that PARs will only evolve under three kinds of circumstances: (i) there are strong timing constraints on the cue and the environmental status, (ii) delaying development is costly, and development time is either fixed or slow development is costly, or (iii) when the period between the cue and the eventual environmental change is variable and the cost of not completing development before the change is high. These predictions are empirically testable.

Introduction

Phenotypic plasticity is ubiquitous in the biological realm,[1,2] and it has fundamental consequences for our understanding of development and its evolution. Much theoretical research on plasticity has focused on the circumstances under which plastic responses are favored over specialization (e.g., Refs. 3–5). A slightly different question can be asked about the sort of plastic response that might be mounted, perhaps under the assumption that a plastic response of some kind will be selectively advantageous. (This assumption seems justified because if plasticity is not favored, it will presumably not have evolved.) Gabriel et al., for example, investigated the conditions leading to the evolution of reversible plasticity;[6] Padilla and Adolph modeled the relative advantages of responding to an environmental cue after various time lags;[7] the question of how the periods that are sensitive to the environmental cue(s) might evolve was investigated by Panchanathan & Frankenhuis.[8]

The realization that the phenotypic development of the induced response need not manifest itself immediately after the environmental cue has generally been under-appreciated by evolutionary biologists (but see Ref. 7). Such a delay may have important consequences for fitness, and indeed, some authors have argued that a number of phenotypic changes observed in adult humans that lead to deleterious health effects (e.g., diabetes, hypertension) are in response to later environmental states that were not predicted earlier in life, when the individual was a fetus or newborn.[9–11] Gluckman et al. have further claimed that the physiological mechanisms underlying many of these delayed responses have an adaptive basis and have labeled them "predictive adaptive responses" (abbreviated PARs).[10,12,13]

PARs are a form of developmental plasticity but differ from most in that the selective advantage of the response manifests itself later in life, well after the initiating environmental cue has disappeared and development of the induced phenotype has completed, when a second or "eventual" environment prevails.[12,13] Note that this eventual environment need not be the same as that which induced the initial response, which itself need not be immediately advantageous. This situation contrasts with most cases of phenotypic plasticity, in which the response to the

cuing environment occurs straight away and the adaptive response is appropriate to that same environment.

An illustrative case of a PAR is adult coat thickness in the Meadow Vole, *Microtus pennsylvanicus*, which is induced before birth by the day length sensed by pregnant mothers, but which has an evolutionary pay-off in the highly seasonal post-natal environment where temperature is the selective agent.[14,15] Critically, the inducing environmental cue is no longer apparent when the response is first manifested, let alone when this response is selectively favored. Nor is there usually a benefit to a fetus or neonate of having a thicker coat; the advantage comes later in life.

A second example of a PAR involves the Desert Locust, *Schistocerca gregaria*, which exhibits two quite different adult morphs, a solitary and a migratory form. Larvae developing from eggs laid by females from low-density populations grow into solitary adults with small wings that eat a specialized diet, which is advantageous when food is plentiful.[16,17] Larvae from high-density populations become the migratory morph with large wings and a more generalized diet, more suitable when food is scarce.[16,17] Note that there is no immediate advantage to the larvae emerging from the eggs from this developmental decision; the selective benefit arises only after the larvae have metamorphosed into adults.

In humans, as mentioned above, PARs induced by a misleading cue are thought to underlie a number of diseases, most notably the suite of conditions known as metabolic syndrome.[10–13] Two different manifestations of severe acute malnutrition, kwashiorkor and marasmus, provide a further example. The two conditions are more likely to arise in children with higher versus lower birth weights, respectively. The protein and lipid metabolism in marasmic children is relatively thrifty compared to those with kwashiorkor, and their long-term survival is greater.[18] This difference is consistent with the hypothesis that babies with lower birth weights have developed a thrifty phenotype in response to cues received *in utero* that suggest the adult environment is likely to be restrictive.[18]

At this point, we should make a nomenclatural clarification that what we call a PAR has been called by others an "external PAR" in contrast to what they term an "internal PAR."[19,20] This latter form of plastic response occurs not because the environmental cues forecasts the eventual environment, but because the early-life environment has irreversible phenotypic consequences, such as limiting growth. These forms of plastic response are clearly conceptually distinct, although they are not mutually exclusive evolutionary explanations. We confine ourselves to modeling "external PARs."

A number of theoretical questions are raised by the above suggestions, most critically, "Why wait?" The gap between the cue and the benefit would seem to allow too easily for a mismatch between the prediction of the cue and the eventual environment in which fitness is evaluated (as is seen in the examples of metabolic syndrome that motivated these ideas). A more proximal cue would surely be more accurate and, hence, everything else being equal, one would expect selection to use cues that occur closer to the time when development should be initiated. In brief, there should be no delay in the development of the induced phenotype.

A second issue with waiting is that the maintenance of the induced response is almost certainly costly; if it were not, then the response should be constitutive, developing under all circumstances. (Note that the maintenance cost is separate from that of developing the induced response, both of which are different from any cost of the ability to be plastic. Whether or not this last cost is significant, or even real, has been a controversial issue.[21,22]) Hence, the response should be completed as close to the time when it confers a selective advantage. In other words, the induced phenotype should not anticipate the eventual environment.

A significant advance was made by Nishimura, who derived a model of an inducible phenotype, which developed after a delay in response to an environmental cue.[23] The optimal evolutionary outcome resulted from a balancing of the increased costs but reduced death rate of the induced phenotype. Rather counter-intuitively, non-zero delays were favored under a variety of scenarios. By determining the delay for which fitness was maximized, Nishimura found that longer delays were favored under a number of conditions: when the benefit of the induced phenotypes was smaller, when the cost of developing and maintaining the induced phenotype was higher, when the time required to develop the induced phenotype was shorter, and when the organism starts with few energetic resources and fitness is evaluated at a distant time. This model was extended to deal with uncertainty in energy availability, death rates, and waiting times for frequency distributions typical of natural populations by Wake et al.[24]

Nishimura's model and its findings cannot be applied directly to our above "Why wait?" questions for PARs because it assumes the environmental cue is simultaneous with the change in environment to that in which fitness is evaluated and hence does not allow the induced phenotype to complete development before the onset of that eventual environment.[23] In a PAR, in contrast, the cue occurs well before the advent of the eventual environmental state during which fitness is evaluated, and the induced phenotype anticipates this second environment.

Nishimura's model also makes a number of rather restrictive assumptions. In particular, it assumes that there is no effect of responding to the cue until development is complete and the induced phenotype manifests itself. In other words, (i) the cost per unit time of developing the induced phenotype was the same as the background cost and (ii) the death rate during development was similarly unchanged from that during the delay. A second restrictive assumption of Nishimura's model was that the development time was constant. But both the delay and development times are potential targets for selection, and they are unlikely to be independent of each other because the total time between the detection of the cue and the manifestation of the induced phenotype may also be important. Just how much time is allocated to these two periods will depend on the costs (or possible benefits; see Discussion) of the delay and developing, as well as just when and how much of the benefits of the induced response begin. We note that in many systems, this total time is all that can be observed and it may be difficult or impossible to decide whether a positive delay has been selected or if speeding up development is too costly. The cost of development may depend not only on the induced phenotype itself, but on how quickly that phenotype must be developed.

Here, we develop an optimality model of a single population that applies to the question of waiting times for PARs to be fully manifest in the eventual environment. Our model is different from many others examining the evolution of various forms of phenotypic plasticity (e.g., Ref. 5,25) in that it breaks the time between the initiating environmental cue and the start of the "eventual" environment into segments and examines how selection impacts the duration of those segments.

Model

As shown in Fig. 1, we assume that after an environmental cue is detected, the organism waits for a time t, which we call the "delay,"

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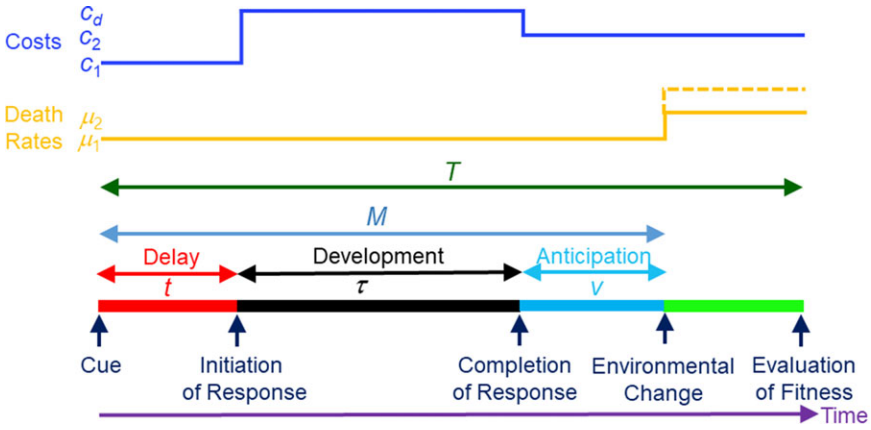


Fig. 1. Life history of the model organism. The period between the cue and the environmental change is fixed and partitioned into three periods: delay, development, and anticipation. Costs per unit time are shown in blue: c_1 during the delay, c_d during development, and c_2 afterward. Death rate is shown in yellow: μ_1 until the environmental change and μ_2 afterward. The dashed yellow line shows the death rate for an organism that fails to respond to the environmental cue.

before initiating development of the induced phenotype, which completely manifests after a period τ, which we call "development." Of course, this partitioning of time is somewhat arbitrary, as at the very least some molecular changes are surely induced immediately by the cue. Nevertheless, in many cases, obvious developmental changes are not observed until well after the cue, perhaps because those changes build on features not yet present in the developing organism, and it is this period we characterize as the delay. In the meadow vole example, for instance, t is the time between the mother's perception of the critically short day length and the initiation of the growth of the fetal fur coat, and τ is the time from that point until the completion of fur growth before birth. During the delay, the constant per unit time cost of the yet to be induced phenotype is c_1, and the per-capita death rate μ_1 is also constant. During development, the cost of development per unit time is higher and so c_1 is replaced by c_d but, because the environment is unchanged, the death rate is unchanged.

The completion of development (i.e., the manifestation of the induced phenotype at a time $t+\tau$ after the cue) anticipates the environmental change (to the eventual environment) by some time v, a period we call "anticipation." In the case of the meadow vole, v is the time from the completion of fur-coat growth until the onset of cold weather in which the thicker coat is a selective advantage. Note that the sum of these three periods (delay, development, and anticipation, $t+\tau+v=M$) is fixed as it is the time between the environmental cue and the onset of the eventual environmental state, both of which are outside the control of the organism (and not immediate targets of selection). After development is complete, the cost rate becomes c_2 and, after the environment changes, the per-capita death rate becomes μ_2. Note that, because we assume that plasticity is favored, μ_2 is less than the value that would apply to an un-induced individual (indicated by the dotted line in Fig. 1). This inequality means that a phenotypic response is advantageous and backs up our implicit assumption that a response will occur. Moreover, the dotted line implies that any response that is not completed by the time the eventual environment obtains is unequivocally disadvantageous, compared to development that completes at or before this time. This comparison matters when we consider the effect of any variation in this timing below (see Discussion). Note that the biology requires all these parameters to be non-negative. Furthermore, costly development implies that $c_d > c_2 > c_1$.

Fitness is evaluated at time T ($\geq M$). We assume that fitness can be measured using the product of the probability of survival to time T and the energy at that time.[23] We are interested in the conditions under which selection should favor a delay (i.e., $t>0$) and when anticipation should be favored (i.e., $v>0$). In other words, what values of t, τ, and v maximize fitness? Because M, the sum of delay (t), development (τ), and anticipation (v) is fixed, we arbitrarily use the first two as our independent variables, without any loss of generality. We further assume that the total initial energy budget is a constant, E, which is reduced during each period by the product of the cost rate and the length of that period.[23] Hence, at time T, the remaining energy is

$$E-(c_1t+c_d\tau+c_2(T-t-\tau)). \tag{1}$$

Similarly, the probability of survival is

$$\exp[-(\mu_1(t+\tau+v)+\mu_2(T-t-\tau-v))], \tag{2}$$

and hence the fitness function is

$$W(t,\tau,v)=e^{-\mu_1(t+\tau+v)}e^{-\mu_2(T-t-\tau-v)}[E-(c_1t+c_d\tau+c_2(T-t-\tau))]. \tag{3}$$

We investigated five different yet simple forms of development, illustrative of possible realistic ways in which developmental costs may occur (see Table 1 and Fig. 2 for a summary). Under option (a), we assume a fixed developmental time, τ, during which c_d is also a constant. Hence, the total cost of development is also a constant, $c_d\tau=D$, say. Under option (b), we assume that there is a fixed developmental cost, D, in addition to the background cost per unit time, and so the total cost of development is $c_1\tau+D$. Longer development would be costlier if, for example, the cellular machinery underlying development was expensive to maintain.

It is also conceivable that shorter (i.e., faster) developmental time incurs a greater cost (in addition to the background rate), perhaps because rapid development requires significant energy and/or nutrient inputs in a short period. We implement such a cost in option (c), where we assume, for simplicity, a type of Michaelis-Menten response,[26] so that the total cost of development is $c_1\tau+k_1(2k_2+\tau)/(k_2+\tau)$, where k_1 and k_2 are positive constants (with appropriate units of cost per unit time and time, respectively). Under option (d), we allow both rapid and slow development to be costly, making the total cost of development $c_1\tau+k_1(\tau-k_2)^2$, where again k_1 and k_2 are positive constants (with appropriate units of cost per unit time and time, respectively).

Finally, under option (e), we assume that delaying development bears an increasing cost. Such modifications seem quite plausible

https://doi.org/10.1017/S2040174420001361 Published online by Cambridge University Press

Table 1. Summary of Models

Model	Cost of development	Optimal times
A	Constant, D	τ is fixed; $t = M - \tau$, $v = 0$ (assuming $c_2 > c_1$)
B	Increasing function of development time: $c_1\tau + D$	$t + \tau = M$; $v = 0$
C	Faster development is expensive: $c_1\tau + k_1(2k_2 + \tau)/(k_2 + \tau)$,	$t = 0$, $\tau = M$, $v = 0$
D	Fast & slow development are both expensive: $c_1\tau + k_1(\tau - k_2)^2$	$t = M - k_2$, $\tau = k_2$, $v = 0$
E(A)	Delay is costly: $c_{d1}t + D$ or	τ is fixed; $t = M - \tau$, $v = 0$ (when $c_1 + c_{d1} < c_2$) τ is fixed; $t = 0$, $v = M - \tau$ (when $c_1 + c_{d1} > c_2$)
	$c_{d1}t^2 + D$	τ is fixed; t, $v > 0$ is possible
E(B)	Delay is costly: $c_{d1}t + c_1\tau + D$	$t = 0$, $\tau = M$, $v = 0$
E(C)	Delay & fast development are costly: $c_{d1}t + c_1\tau + k_1(2k_2 + \tau)/(k_2 + \tau)$	$t = 0$, $\tau = M$, $v = 0$

because delaying development of one character (or suite of characters) may impact many other aspects of the organism's development, which may be costly. Alternatively, there may be a cost to "remembering" the cue until development begins. We incorporate this assumption into our model by modifying the developmental cost in one of the previous options to include a term that is an increasing function of the length of the delay, so that, for example, modifying option (a), D is replaced by $c_{d1}t + D$, where c_{d1} is a positive constant. Incorporating costly delay into option (c) (in which fast development is expensive) is interesting because, everything else being equal, delaying development directly shortens the time available for development and probably speeds it up.

In all cases, our exact choice of function is arbitrary and chosen to illustrate various different ways developmental cost can be incurred (see Fig. 2). Options (a) – (d) are implemented as Models A – D; the possible modifications under option (e) as, for example, Model E(A).

Our formulation assumes the cue is always detected and is perfectly reliable. It is important to realize that the evolution of plasticity may be favored even when these two assumptions are violated.[3,5] Nevertheless, selection will favor cues that are correctly detected and reliable, since such cues will maximize the benefits of the induced response (but see Ref. 27). Moreover, Nettle et al. have argued that PARs as we have modeled them (what these authors call "external PARs") evolve only when cues are highly accurate.[19] For both these reasons, our assumptions are likely to be more than reasonable. We discuss potential consequences of unreliable cues below.

Our analyses are algebraically messy (see Supplementary material) but conceptually simple. We want to maximize the fitness function $W(t, \tau, v)$ given by equation (3), subject to the constraints that the sum of these three variables (M) is fixed and that times cannot be negative, etc. We thus have a standard two-variable constrained maximization problem, and we arbitrarily choose to carry out the differentiation with respect to t and τ, ensuring we also investigated fitness values on the boundaries of allowable variable space (e.g., when $t = 0$). We summarize variable names, our optimization process, and the constraints that apply in Table 2. The algebraic details of the optimization process may be found in the Supplementary material.

Results

When development time, τ, and developmental cost, c_d, are fixed as in option (a), the problem reduces to a single-variable calculus problem. We need to maximize fitness, subject to the condition that both t and v are non-negative. It is straightforward to show (see Supplementary material, Model A) that the fitness is maximized when the length of anticipation (v) is zero. This result is perhaps not surprising, given that the cost of the induced phenotype is greater during anticipation than during the delay ($c_2 > c_1$), whereas the death rate remains the same (μ_1). If, for some reason costs decreased after the completion of development, this result is reversed and the delay should reduce to zero in order to maximize fitness.

When, as under option (b), development incurs a fixed cost over the background rate (i.e., development cost $= c_1\tau + D$), the problem requires maximizing a function of two variables with a constraint. Again we find (see Supplementary material, Model B) that fitness is maximized when the anticipation time (v) is zero. This result obtains because, as in option (a), anticipation has the highest cost per unit time. Any combination of delay (t) and development time (τ) that sums to the fixed period between the cue and the onset of the environmental change (M) is sufficient to give this optimal result. This equivalence between the times for delay and development arises because the marginal cost of each of these times is the same, c_1.

In our formulation of rapid development being expensive (option (c), in which development cost $= c_1\tau + k_1(2k_2 + \tau)/(k_2 + \tau)$), we find that fitness is maximized when all the available time (M) is allocated to development, eliminating any delay or anticipation (see Supplementary material, Model C). Again, this result appears intuitively reasonable: anticipation is more expensive per unit time than delay, and switching any remaining time from delay to development is cheaper because the cost of development is minimized when it is as long as possible.

Under option (d), when intermediate development times are cheapest (development cost $= c_1\tau + k_1(\tau - k_2)^2$), fitness is maximized when the above-background developmental costs are minimized, which occurs when $\tau = k_2$. This fitness maximum also requires no anticipation, again because $c_2 > c_1$; any remaining time is assigned to the delay (see Supplementary material, Model D).

Adding a term to make delay increasingly costly (option (e)) can change results dramatically. When modifying option (a), in which development time, τ, is fixed to include a cost proportional to the length of the delay, we have total development cost $= c_{d1}t + c_d\tau$ and still have a single-variable problem. It can be shown (see Supplementary material, Model E(A)) that when $c_1 + c_{d1} < c_2$, the above result is unchanged (i.e., fitness is maximized when $v = 0$), but when $c_1 + c_{d1} > c_2$, fitness is maximized when the delay is zero ($t = 0$). Effectively, the cost per unit time of the delay is increased by c_{d1}. If the cost of delay is not linear – say we assume development cost $= c_{d1}t^2 + c_d\tau$, which increasingly penalizes longer delays – the situation is algebraically more complicated, and a fitness optimum can occur when t and v are both non-zero.

When delaying is costly, the equivalence between the marginal cost of delaying and developing in option (b) vanishes and the optimal solution is for no delay (or anticipation): all time should be allotted to development (see Supplementary material, Model E(B)). We obtain the same result for option (c), when delaying

https://doi.org/10.1017/S2040174420001361 Published online by Cambridge University Press

Table 2. Summary of Constrained Optimization Process

Symbol	Meaning	Constraints
t	Delay = time between environmental cue and initiation of development	$0 \le t \le T$, $t+\tau+v=M$
τ	Development = time from initiation of development until completion of induced phenotype	$0 \le \tau \le T$, $t+\tau+v=M$
v	Anticipation = time from completion of development until start of eventual environment	$0 \le v \le T$, $t+\tau+v=M$
M	(constant) time between environmental cue and start of eventual environment	$t+\tau+v=M$
T	(constant) time at which fitness is evaluated	$M \le T$
E	(constant) total initial energy	$0 \le E$
c_1	(constant) energetic cost per unit time during delay	$0 < c_1 < c_2$
c_d	Energetic cost per unit time during development. Different options (Table 1) assume different formulations for c_d	$c_2 < c_d$
D	Fixed cost of development under options (a) and (b)	$0 < D$
k_1, k_2	Positive constants for function of costs of development under options (c) and (d)	$0 < k_1, k_2$
c_2	(constant) energetic cost per unit time after development is complete	$c_1 < c_2 < c_d$
μ_1	(constant) per-capita death rate before start of eventual environment	$0 < \mu_1$
μ_2	(constant) per-capita death rate after start of eventual environment	$\mu_1 < \mu_2$
W	Fitness, a function of t, τ, and v, given by equation (3)	$0 \le W$

The optimization process consists of finding the maximum of W, given the above constraints, for different formulations for c_d outlined in Table 1. Although W appears to be a function of three variables, the constraint $t+\tau+v=M$ means that there are just two independent variables, arbitrarily t and τ.
Hence, the optimization process amounts to proceeding through the following steps:

- Finding the maximum value of the fitness function $W(t, \tau)$ given by (3) on the triangular state space
  $\Omega = \{ (t, \tau) : \ 0 \le t, \ \tau, \ t+\tau \le M \}$,
  noting that the independent variables are choices of strategies, not evolving time.
- We solve $\frac{\partial W}{\partial t} = \frac{\partial W}{\partial \tau} = 0$ for t and τ on Ω, and check that the solution is indeed a maximum (rather than a minimum or a saddle point).
- We must also check the boundaries (including the corners) of Ω for potential maxima. To do so, we (i) set $t = 0$ and solve $\frac{\partial W}{\partial \tau} = 0$, (ii) set $\tau = 0$ and solve $\frac{\partial W}{\partial \tau} = 0$ and (iii) set $\tau = M - t$, and solve $\frac{\partial W}{\partial \tau} = 0$ and (iv) evaluate $W(0, 0)$, $W(M, 0)$ and $W(0, M)$.

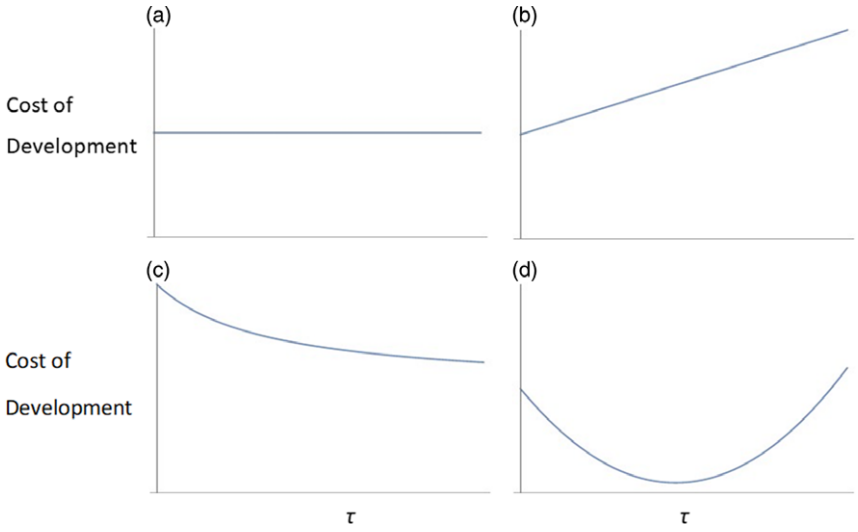


Fig. 2. Possible costs of development. Options for the cost of development as a function of developmental time (τ). Graphs a–d show the shapes of possible cost options that are modeled, respectively, by Models A–D of Table 1.

development is both directly costly and shorter development time is more expensive (see Supplementary material, Model E(C)).

Discussion

PARs are a form of developmental plasticity characterized by the temporal separation of the inducing signal (usually some environmental cue) and the commencement of the "eventual" environment to which the induced phenotype is adapted. The time between the signal and the eventual environment is, in principle, divisible into three periods: (i) a delay between the cue and the initiation of development, (ii) development, and (iii) the anticipation of the eventual environment after the completion of development. Our modeling gives insight into how this partitioning is likely to evolve under various scenarios concerning the costs of development.

Our models show that, for a variety of formulations for the costs of development (options (a)–(d)), PARs maximize fitness when there is no anticipation. For the meadow vole example, this finding suggests that thicker coat development should be timed to be

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completed just as the cold weather (in which the thicker coat is selectively advantageous) begins. This result holds provided delay has no intrinsic cost (and in some cases when is not too costly) for all the cases of developmental cost we investigated, and follows from our assumption that the induced phenotype has a maintenance cost (in addition to any background costs) and hence anticipation is expensive. We suggest, therefore, that many PARs will not exhibit anticipation.

In addition, when rapid development is costly (option (c)), fitness is maximized when there is no delay between the environmental cue and the initiating of development, and hence all available time is allotted to development. In the case of the meadow vole, this absence of delay would mean that the thicker coat should begin to develop as soon as the shorter day lengths are sensed by the mother. Developmental costs are thus privileged, fitness being maximized whenever the additional costs of development are minimized.

If delay is not inherently costly, but both rapid and slow development are (option (d)), the available time is split between delay and development, with the exact proportions depending on the details of these costs. In this scenario, the meadow vole's coat would not begin to develop immediately the mother sensed shorter days, but it would still not complete until the onset of winter.

The most interesting results are found when the developmental time is fixed, perhaps as a consequence of the complexities of development (option (a) and (e(a))). When delay is cost-free (option (a)), there is no anticipation and delay takes up the remaining time. When delay is costly, however (option (e(a)), the outcome depends on the details of these costs: it is possible for zero delay, zero anticipation, or non-zero delay and anticipation to be optimal, depending on parameter values.

At first glance, these results appear paradoxical: features of many examples of PARs – non-zero anticipation and, usually, a delay before the development of the induced phenotype can be observed – do not correspond to the maximizing of fitness. Nevertheless, our modeling of option (e(a)) shows that if developmental time is constrained and delaying it is expensive (as might be the case if, for example, the suite of induced characters affects the development of other features of the organism), a classical PAR may be optimal.

Several further explanations for this paradox are possible. First, PARs may be highly unusual. For instance, they may be evolutionarily transient, in the process of being eliminated as selection moves the system toward the optimum. Alternatively, they may only evolve under restrictive conditions: for example, Nettle and colleagues found that the evolution of PARs required accurate and reliable cues.[19,20] The well-documented occurrence of PARs in nature, however, suggests that this explanation is unlikely.

Second, PARs may be subject to constraints not incorporated into the above modeling. Most simply, for example, development might not be able to be initiated until some other developmental stage is complete, or it might have to be completed by certain times in order for some other developmental process to have sufficient time, forcing the delay or anticipation times to be positive: $t > 0$ and $v > 0$, respectively. In the meadow vole's case, for instance, thicker coat development might not be able to be initiated as soon as the mother is subject to shorter days because fetal development has not yet reached the stage at which hair can grow. More generally, perhaps, the induced phenotype may be strongly unfavorable in the environment immediately following the cue, conferring its benefit only in the eventual environment. Kuzawa has posited that such a scenario occurs in humans,[28] who anticipate poor nutritional conditions in childhood or beyond, when insulin resistance would be expected to be advantageous (see also Ref. 13). For neonates, however, insulin sensitivity may be advantageous because it allows for greater adipogenesis and, indeed, this is what is observed.[29] This sort of constraint could be incorporated into the model by increasing the death rate after the completion of development (i.e., after time $t + \tau$) during the period of anticipation to some value, $\mu_a > \mu_2$. Such a change would clearly make a non-zero anticipation even less likely. Both of these explanations suggest that classical PARs arise only in very restricted circumstances, perhaps in taxa with complex (and thus highly time-constrained) development occurring over very different environments. This scenario characterizes mammalian development where fetal and infant environments are very distinct from post-lactational environments in terms of nutrition, predator risk, thermoregulation, etc.

Third, the models of development we use may be too simple: costs may depend on the organism's age or they might not be independent of the death rate. This explanation seems unlikely in that our results are robust to very different formulations for developmental costs, although there is one notable exception, namely when delay itself is expensive (option (e)).

Finally, PARs may depend on variation in the timing of the onset of the eventual environment (i.e., effectively variation in M), especially if individuals whose development is incomplete when this event occurs have a higher death rate, as indicated by the dashed yellow line in Fig. 1. Such individuals are always at a selective disadvantage compared to any that have completed their induced response. Thus, even if anticipation incurs some cost, the benefit of avoiding the far greater cost of completing development late more than compensates. This explanation seems by far the most plausible biologically and, indeed, it fits with observations on children with marasmus or kwashiorkor in Jamaica.[18] The former appears to be pre-adapted to survive malnutrition, as indicated by their low birth weight, whereas the latter have much higher mortality from their experience of infant malnutrition.[13,18] In the case of the meadow vole, the onset of cold weather will vary from year to year, sometimes by quite a margin. We note, too, that there is theoretical support for such an explanation: Wake et al. showed that in a stochastic extension of Nishimura's model,[23] selection led to a trade-off between the mean waiting time of a population and the variance in that waiting time.[24] The model of Panachanathan & Frankenhuis suggests a related reason for the evolution of the waiting inherent in PARs, namely, inaccurate or unreliable cues.[8] As is the case with variable timing, delaying development when cues are unreliable may reduce the cost of any environmental mismatch.

Our findings suggest several hypotheses suitable for empirical testing. Our models imply that PARs may be relatively unusual, possibly characterized by constrained developmental windows. The observations surrounding human neonates' insulin sensitivity and adiposity seem to fit well here. And, PARs may often be an appropriate response to the variable onset of the eventual environment (or even variable independence from the mother in mammals) predicted from by an early-in-life cue. The PARs thought to underlie a greater risk of metabolic syndrome (arising from an inaccurate fetal or infant cue) certainly seem to fit this last prediction. The eventual nutritional environment to which the individual is adapted could well arise at different ages. Moreover, we would expect the maternally experienced day length that triggers

https://doi.org/10.1017/S2040174420001361 Published online by Cambridge University Press

the development of thicker coats in the meadow vole to be longer in colder areas.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S2040174420001361

Acknowledgements. We thank Yoh Iwasa, Willem Frankenhuis, Sam Scheiner, and anonymous reviewers for suggestions that greatly improved the clarity of the manuscript.

Financial support. This work was supported by Gravida, the National Centre for Growth & Development, funded through the Centres of Research Excellence Fund of the New Zealand government's Tertiary Education Commission.

Conflicts of interest. None.

Ethical standards. None.

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