Design sans adaptation

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Abstract

Design thinking in general, and optimality modeling in particular, have traditionally been associated with adaptationism—a research agenda that gives pride of place to natural selection in shaping biological characters. Our goal is to evaluate the role of design thinking in non-evolutionary analyses. Specifically, we focus on research into abstract design principles that underpin the functional organization of extant organisms. Drawing on case studies from engineering-inspired approaches in biology we show how optimality analysis, and other design-related methods, plays a specific methodological role that is tangential to the study of adaptation. To account for the role of these reasoning strategies play in contemporary biology, we therefore suggest a reevaluation of the connection between design thinking and adaptationism.

Keywords

Design thinking
Adaptationism
Reverse engineering
Heuristic
Optimality

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1. Introduction

Appeals to design in biology are often thought to entail a process of design. In pre-Darwinian thought, such concepts were frequently presumed to derive content from a divine intelligent designer. But in modern biology, too, design and related notions are common, and thought to have a basis in the designed structure's history of evolution by natural selection. In some views, the appeal to design can be justified on adaptationist grounds, as a consequence of the centrality of selection (and its products) in the biological world (Dawkins 1976; Parker and Maynard-Smith 1990; Williams 1966). It has even been argued that, at some level, employing analogies between organisms and artifacts is inescapable (Dennett 1995). In contrast, others have criticized the tendency for design thinking, seeing in it a bias against non-selective factors such as genetic drift and the availability of variation (Gould and Lewontin 1979; Jacob 1977; Lynch 2007; Griffiths 1996; Richardson 2007). Either way, design and kindred notions are often linked closely to the search for, and elucidation of, a biological trait's history of natural selection. As the title suggests, our goal in this paper is to show that the link between design and adaptation is not as strong as it may appear to be. As we will demonstrate, the cognitive strategy of design thinking in general, and reverse engineering in particular, can be detached from the study of natural selection. It need not be grounded in adaptationist presuppositions.

To make this case we first identify a concept of design that has a present-looking, thin character and does not itself entail a designing process. We demonstrate its use by looking at studies that target so-called design principles:

generalizable patterns of organization which play a role-functional part in present-day biological systems. We then suggest that in the study of design principles (and in related contexts), tools often associated with adaptationism—most importantly, optimality analysis—may take on a different role, serving as search tools rather than embodying adaptationist assumptions.

While we urge a distinction between design-inspired analysis and the search for adaptation, we do not wish to deny that the two types of analysis are often combined, and fruitfully so. Rather, our goal is to explicate a hitherto unacknowledged role for design-related methods, thereby weakening the tendency to see the presence of such methods as indicative of adaptationism and ~~kindred~~associated theoretical stances.

The paper is structured as follows. In Section 2 we introduce a thin notion of design and discuss the way in which it figures in the study of design principles. Section 3 discusses two examples, both of which involve design-inspired analyses of a closely related biological system, but do so in starkly contrasting ways. The first example illustrates the familiar role of design-related notions as part of an adaptation-oriented analysis. The second embodies the kind of work we see as novel, namely a methodological, search-constraining use of optimality. Section 4 generalizes the lessons drawn from these examples. Section 5 summarizes our argument and discusses a possible objection.

2. Being designed versus having a design

A growing body of research now focuses on what many biologists refer to as *design principles* of biological systems (Alon 2007; Poyatos 2012; Salvado et al. 2011; Savageau 2001). In this context, the term ‘design’ refers to patterns of organization that can be specified abstractly, supplying an explanation for a given behavior that occurs across a range of cases in which the organizational pattern is realized.[1] A couple of examples will illustrate what we mean. As championed by the cyberneticists, a design embodying negative feedback provides a means of maintaining concentrations of a system’s ingredients within a target range (Wiener 1948). Engineers also demonstrated that negative feedback generates oscillations that can, under some circumstances, be sustained indefinitely. Accordingly, biologists often search for evidence of negative feedback when they discover that a system behaves in similar ways. In

recent years biologists have discovered a host of similarly simple design principles and established the functions they generate. For example, Tyson et al. (2003) showed that a network of two units both feeding back on each other is capable of producing a bi-stable switch that requires a higher level of input to turn on than to turn off. They argue that such a switch can enable a system of otherwise reversible operations to proceed in just one direction. They then appealed to particular realizations of this design to explain specific aspects of the regulation of the cell cycle. As these examples illustrate, to say that a system has a given design is sometimes a way of saying that it (presently) exhibits a certain organizational pattern, one that may play a comparable role in other systems. Thus, isolating a system's design may be a part of explanations that target the causal structure of extant systems, and need not embody historical assumptions about its origins.[2]

To be sure—and we shall come back to this below—an object's design, in this thin sense, may (and often does) have its origins in a *process* of design. Natural selection, or a flesh-and-blood engineer, may be responsible for negative feedback or whatever the system feature at issue may be. But identifying and analyzing a design does not, as such, embody commitments on this score. A system may owe its design to historical constraints or even to chance. It may have been put together or selected for a certain reason, yet have a design that is conducive to some other function (we address notions of function in Section 4). In sum, the notion of design we describe does not imply a designer of any kind. One way to express this is to say that we are interest~~ing~~ed in a system's *having* a design—and the tools used to understand its design—rather than *being* designed.

Although bridges to engineering and appeals to design principles have a long history in some parts of biology, they have become far more widespread in the last two decades, as methodological tools from engineering disciplines other than mechanical engineering have been explored in biology. In part, the increasing importance of mathematical modeling and engineering methods in biology, such as network modeling, reflects a frustration that the discovery of more and more parts and low-level activities in biological mechanisms has not shed sufficient light on how biological mechanisms actually work (Lazebnik 2002). The hope of biologists pursuing design principles is that the sort of understanding an engineer provides will fill this gap. One key characteristic of

the engineer's perceptive is that it tends to operate at a certain level of abstraction—engineers have the mindset, and the tools, to move beyond low-level structural-material specification and to look at more skeletal organizational features, often mathematically. In these respects, engineers often sit mid-way between the fundamental physicist and the traditional molecular biologist. The former seeks highly abstract and general, often formal, descriptions, whereas the latter looks at the details of concrete systems and typically produces informal, verbal and/or graphical representations. Seen in this light, the invocation of design-related notions is indicative of a present-looking mindset and an associated toolkit rather than an interest in uncovering historical origins.

These points are equally pertinent in "forward" engineering, devoted to producing artifacts with a specified functionality, as they are to reverse engineering, in which the goal is to figure out the role of some feature of a preexisting system. The concept of reverse engineering was initially associated with attempts to copy military hardware without having access to the design protocol. It acquired more currency as software engineers confronted the problem of understanding and improving older software systems once the original programmers could no longer be consulted (Chikofsky and Cross 1990). The strategy of reverse engineering has also come to be employed in order to facilitate the re-use of components or design strategies across different engineered systems. Except in synthetic biology, the aim of biologists in investigating design principles is not to reuse these principles in new organisms. But they nonetheless often hope to generalize across contexts, in explaining different (extant) biological phenomena. Accordingly, one sees a tendency in recent mathematical and "systems" biology to emphasize the search for design principles (Hartwell et al. 1999; Alon 2003) and to use the language of reverse engineering (Csete and Doyle 2002).[3] More importantly, such a-historical appeals to engineering do not serve merely to frame research or to liven-up the presentation of results; they affect specific research strategies. To bring this out, we first discuss in some detail two concrete examples. Afterwards, we return to a more general discussion.

3. Two contrasting examples

In this section we describe two closely related cases: both target the same system and make analogous appeals to design-related concepts, including the

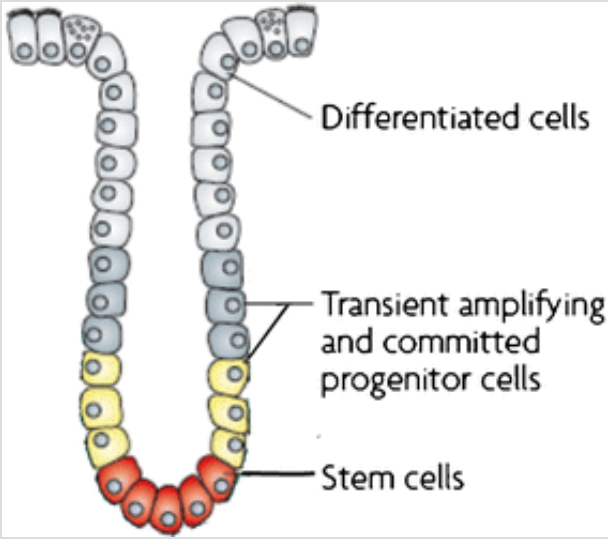
employment of mathematical optimality analysis. Against this background of similarity, we highlight a difference with respect to the relationship between design and adaptation. The first case is geared at the question: what is the adaptive utility of the cellular architecture of intestinal crypts? In contrast, the second case employs design-related concepts and methods in the service of a non-evolutionary mechanistic question, namely: how do intestinal crypts develop?

To begin with, let us provide some background about the system in question: the intestinal crypt in mammals. Mammalian intestines are lined with a single layer of epithelial cells. This tissue forms finger-like invaginations termed *crypts*. There is a vast amount of research on crypts, owing to two interrelated reasons (Humphries and Wright 2008; van der Flier and Clevers 2009). First, colorectal cancer, one of most common causes of mortality in humans, originates in crypts. Second, the epithelium of the intestine is a model for a continuously renewing tissue, in which a small number of stem cells replenish a large pool of transit and mature cells.[4]

Figure 1 illustrates the basic architecture of an intestinal crypt. At the base are a handful of stem cells. The bulk of the crypt is made up of transient and mature cells of which there are several sorts. In an adult crypt, stem cells reproduce asymmetrically to give rise to one stem cell, and one nonstem, i.e. somatic, cell (as we shall see this is not the case in the developing crypt). The somatic cell migrates up the crypt, differentiating along the way into cells that perform various digestive tasks. When a cell reaches the top of the crypt, it dies. This process is very fast; intestinal somatic cells are some of the shortest-lived cells in the multicellular world, with a lifespan of 4–5 days. Such a fast pace of reproduction, together with stress from the harsh chemical environment of the digestive tract, can lead to mutations, unchecked cellular proliferation and carcinogenesis.

Fig. 1

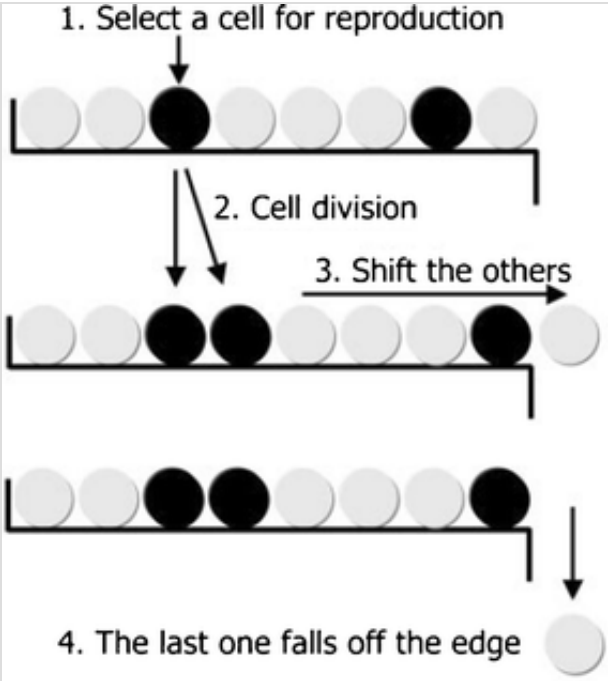
A colon crypt. [Simplified and reprinted with permission from Macmillan Publishers Ltd: Nature Reviews Cancer, Humphries and Wright (2008), Copyright (2008)]



The first case we will look at comes from work by Martin Nowak and colleagues (summarized in Nowak 2006). The broader project that this work is part of seeks to demonstrate that "patterns of cell division in tissues of multicellular organisms have evolved to delay the onset of cancer" (Nowak et al. 2003). One simple model they consider in this context is the so-called *linear process*, illustrated in Fig. 2. This simplified model depicts a crypt as a row of cells. The first (leftmost, in Fig. 2) cell functions as a stem cell, i.e., it has the capacity to produce somatic cells and does so throughout the life of the crypt. The last, rightmost, cell undergoes apoptosis (self-induced death) and is shed into the gut. At each time step, one randomly-chosen cell (possibly but not necessarily the stem cell) reproduces and gives rise to two daughter cells. These push the remaining cells outwards, so that the cell in the next to last position in the crypt "falls over the edge" and dies.

Fig. 2

Nowak's Linear Process model of crypt formation. A randomly selected cell reproduces, pushes other cells to the left, causing the last one to fall off and die. [Reprinted from Nowak et al. (2003) with permission from National Academy of Sciences, U.S.A., Copyright (2003)]



This model makes a number of significant simplifications, but Nowak et al. claim that it "provides a quantitative understanding for how various mechanisms slow down the unwanted somatic evolution that leads to cancer" (Ibid).[5] As this quote implies, the analysis they perform is mathematical. However, we can illustrate the key points informally. To become cancerous, a cell typically needs to accumulate several mutations that, together, lead it to proliferate uncontrollably. Consider first a baseline case in which cells in the colon do not exhibit a stem/soma distinction, and are not compartmentalized into crypts. In this scenario, all cells have the potential to accrue cancerous mutations. If a cell accumulates a mutation that increases its rate of division, it will spread in the intestinal population at the expense of other cells. Assuming that mutations hit cells at random, the progeny of the initially mutated cell, being more numerous than other cells, will have a higher chance of accumulating further cancerous mutations. In this scenario, the progression towards disease is rapid. Its specific likelihood is a function of the degree to which mutations enhance a cell's rate of division and the overall size of the intestinal population.

The Linear process, however, differs in two important ways. First, the intestine is divided into very small compartments, rather than being a large (and well-mixed) population. Second, only the stem cell has long-lived progeny. All other cells have descendants that die as they reach the tip of the crypt. As a

consequence, only mutations that occur in the stem cell will persist for a long period of time, a prerequisite for mutations to accumulate. Thus, the chance of an accumulation of cancerous mutations is not affected by the degree to which such mutations speed up cellular division. Each compartment acts as a small population, in which most mutations occur in "dead-end" lineages. Consequently, the likelihood of a mutation taking over a crypt is very small. As Nowak puts it, the linear process is "the perfect design to protect against mutations in tumor suppressor genes and oncogenes…" (2006, p. 224).

Clearly, this work is adaptation-oriented: it is an argument for a particular selective explanation for the design of colon crypts. In related work Nowak and colleagues discuss more general theoretical considerations supporting the idea that tissue structure is an adaptation against cancer, including arguments from the optimality of this structure, given certain constraints on crypt development. They suggest possible lines of evidence that would bear out this hypothesis—such as comparing the dynamics and structure of epithelial tissues among organisms with different cell division rates, lifespans and related features that affect the size and fecundity of the relevant cell types (Frank et al. 2003). In this case, thinking in terms of the system's design (or "architecture", as they often put it) is clearly associated with an attempt to elucidate the trait's evolutionary basis. The goal of the analysis Nowak et al. offer is to establish that a present-day trait had certain advantages over alternatives, and was selected because of this.

A few comments and clarifications are needed before we move on to describe the second case. First, we do not wish to suggest that Nowak et al. are right in claiming that crypt architecture is an adaptation. Perhaps they have made unreasonable idealizations, or perhaps they draw a comparison with the wrong baseline. Furthermore, Nowak et al. only propose a theoretical argument. They offer suggestions concerning empirical corroboration but they do not carry it out. However, this is neither here nor there for our purposes: what we wish to show is that their work is *aimed at* establishing the adaptive role of tissue architecture and that their use of design-related concepts and methods is in done in this vein.

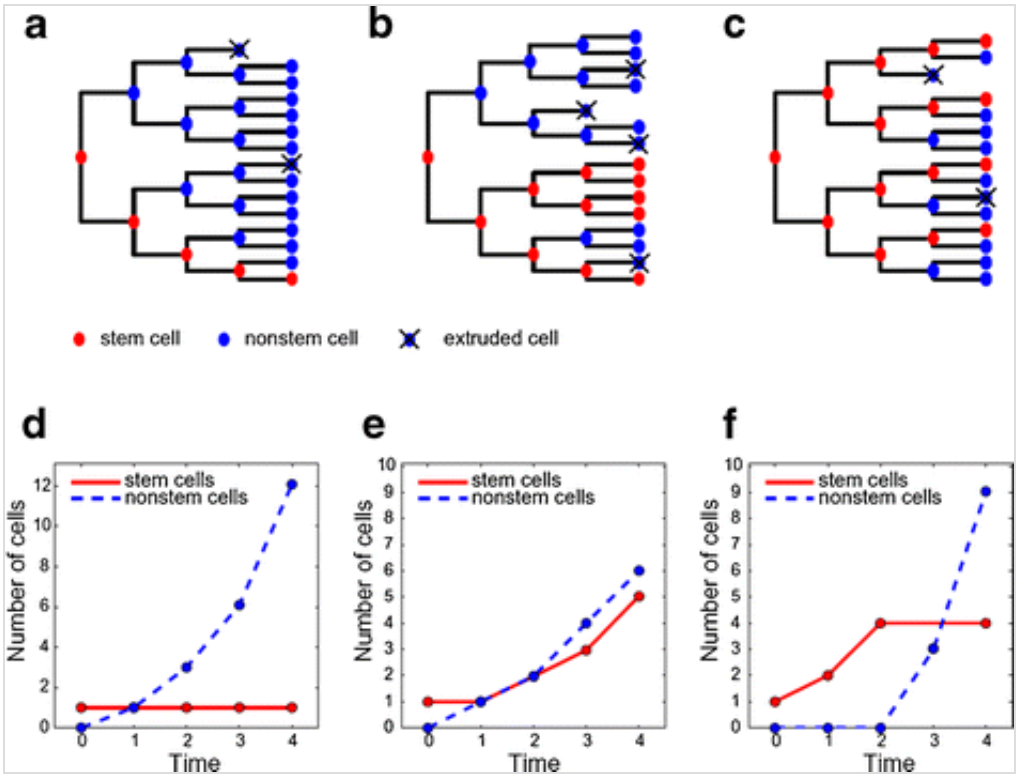
The case we have just looked at contrasts with the type of research we wish to highlight in this paper, namely, work in which design-thinking is *not* geared

towards adaptation, but rather serves as a tool in elucidating present-day causal structure. Here we will look at one central example, involving optimality analysis. Below we will provide a more general discussion and expand the argument beyond the use of optimality. As noted, the case we discuss also pertains to the intestinal crypt. Specifically, it targets the dynamics of crypt *development*. The intestine of newborn mice (commonly used as an animal model in this context) contains no crypts; but they quickly develop postnatally. In a recent paper, Itzkovitz et al. (2012) "use optimal control theory to explore the design principles of the development of…the mouse intestinal crypts." Despite their appeal to notions of design and their use of optimality analysis, these authors do not aim to elucidate the adaptive role of crypt design. Rather, they take as a starting point the idea that crypt development may be optimized with respect to time to maturation,[6] use optimal control theory to derive a solution to this optimization problem, and then test experimentally whether that design is in fact realized. Thus their goal is to elucidate the pattern of cell proliferation that extant mice exhibit. As before, we will describe the results informally.

During development, crypt stem cells can divide either symmetrically, producing two additional stem cells, or asymmetrically, producing one stem and one somatic cell. The question Itzkovitz et al. ask is: what temporal distribution of symmetric versus asymmetric cell divisions optimizes time to maturation? Figure 3 illustrates three generic options: An early phase of exclusively asymmetric divisions, generating a large number of somatic cells early on, which then divide to generate further somatic cells (Fig. 3a, d); an early phase of exclusively symmetric divisions, generating a large pool of stem cells that later generate the somatic cells in a rapid late phase (Fig. 3c, f); and a mixed option, in which there are both symmetric and asymmetric divisions throughout the process (Fig. 3b, e).

Fig. 3

Three possible procedures for generating crypts (**a**, **b**, **c**) and simulation results showing resulting population (**d**, **e**, **f**). [Reprinted from Cell 148(3), Itzkovitz et al. Optimality in the Development of Intestinal Crypts, 608–619, Copyright (2012), with permission from Elsevier]



In this setup, the problem of optimizing time to maturation is equivalent to finding a probability function *p(t)* that specifies the likelihood of a stem cell's dividing symmetrically at any given time point. This is where optimality analysis enters the picture. "The space of possible functions [p(t)] is huge, and analytical methods are therefore essential. By solving this optimality problem", Itzkovitz et al. explain, "we can discern which particular function can achieve the required crypt at the minimal possible time." (Ibid, 610). As it turns out, the optimal solution has a so-called "bang-bang" form, i.e., a dynamic of switching between phases of purely symmetric divisions and purely asymmetric ones. They further show that the fastest bang-bang dynamic arises when rates of division for both stem and somatic cells are at a maximum value. Under this assumption, the optimal solution is achieved by an early phase of purely symmetric divisions, in which the pool of stem cells expands, and then a second phase of purely asymmetric divisions, which generates the somatic cell population.

In contrast to the case we discussed previously, the goal of this work is to analyze the system's present-day causal organization. This is brought out very clearly by what Itzkovitz et al. do next, namely to experimentally verify *whether their model correctly depicts the (current) dynamics of crypt differentiation.*[7] They do so by tracking the number and proliferation rate of

stem cells at different points during development. Using sensitive detection methods, they show that the rate of stem and somatic proliferation is similar and very high; that young crypts are composed entirely of stem cells; that later in development, stem cell production stops and somatic cells begin to proliferate. These and some finer details provide compelling evidence in favor of the dynamic pattern predicted by the optimal control model. Thus the evidence sought concerns the proximal functioning of the crypt and, importantly, not comparative or other evidence pertaining to its relative fitness in the ancestral environment, which would be necessary if the goal were to substantiate a claim about adaptation.

In summary, in Itzkovitz et al. we see a novel role for design-thinking, specifically optimality analysis: it is used as part of an inference as to *how* crypt cells proliferate in the process of maturation. The information sought to validate the model pertains, correspondingly, to mechanistic features of crypt development. On the other hand, no evidence is offered regarding whether this design was an adaptation, nor is there a discussion of evidence that would be needed to support such a claim (as we saw in Nowak et al., above). Moreover, in discussing these results, Itzkovitz et al. state that "other models could give rise to the stem cell dynamics we observed. For example, if stem cells have a protective role for the crypt, the initial formation of the stem cell compartment could enhance the probability of its survival" (Ibid, 617). Here it seems they have in mind the idea that although the proliferation pattern they have established does indeed minimize time to maturation, its existence in mice might be have been favored by natural selection for other reasons, such the protection of crypt stem cells. In this case its optimality properties might simply be a byproduct of other adaptive functions, but this would invalidate neither the analysis nor the empirical discoveries. Thus, Itzkovitz et al. claim to have "uncover[ed] a novel design principle—a temporal order that includes an initial expansion of the entire stem cell pool, followed by a transition to somatic cell production." (Ibid, p. 616) and view this as largely independent of the adaptive role of this design principle.

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4. A new role for design thinking in biology

The research we have just reviewed reveals a new role for design thinking and

associated methods such as optimality analysis—a role that philosophers of biology have not been alert to and that has not figured in existing discussions. The assumption in much of the literature has been that the chief justification for employing optimality models is that biological traits are the product of an optimizing process, namely natural selection. The goal of optimality analysis is then to reveal the selective forces underlying a given trait and to generate predictions which would allow one to test such hypotheses. In this context, the discussion has centered on whether selection is indeed an optimizing force, on how widespread and powerful its role is and on how to carry out and interpret optimality studies (Parker and Maynard-Smith 1990; Orzack and Sober 1994, 2001).

The work we are pointing to uses optimality analysis in an entirely different way: it is part of an investigation of current function, rather than past selection; and its contribution is methodological, rather than embodying assumptions about evolution by natural selection. Let us expand on both aspects in turn.

4.1. Design as a role-function

In philosophy of biology, two central notions of function have been recognized and discussed over the years. With respect to a given feature, we may ask about its *selected-effect* function (its "Wright function"), i.e., about the effect that is causally responsible for the feature's being selected over alternatives in the organism's evolutionary past (Millikan 1989; Neander 1991; Wright 1976). Alternatively, we may inquire into the feature's *role-function* (its "Cummins function"), namely the contribution it makes to the system of which it is an element (Cummins 1975). These two concepts of function are distinct yet compatible (Godfrey-Smith 1994). A feature's selected-effect function has to do with its relative contribution to fitness in the relevant evolutionary past. A feature's role-function is its present-day contribution to some capacity or behavior of a containing system. A feature's current role-function may or may not be the effect due to which it was favored by natural selection. Lewens (2004) coins the terms weak reverse engineering and weak adaptive thinking to identify design-inspired reasoning strategies where the end goal is a non-historical explanation of function. To characterize this type of functions, Lewens suggests a supplement to Cummins' account, called the 'naïve fitness account', which is a nonhistorical account about *current* fitness-contributions.

While our analysis is sympathetic to Lewens' account, our interest does not lie in defending or revising any particular account of what function is but in examining how mathematically defined notions of optimality or design principles can guide functional analysis. While design thinking can play a role in non-adaptationist functional analysis in general, we believe it has a distinctive role in cases in which the design- heuristic takes the form of a mathematically constrained search for possible mechanisms. This point will be clarified below.

According to our thin notion of design, a system's design—the design it has, as it were, rather than what it was designed to do—is the abstract organizational pattern in virtue of which it behaves as it does. In the case of colon crypt development, the design in question is the "bang bang" pattern of cell proliferation. Under this usage, 'design' is a type of role-function: a system's design is a feature that makes a contribution to its overall behavior. For instance, "bang bang" proliferation contributes to the colon crypt's short time to maturation. Now, the contribution in question may also be the design's selected-effect function, i.e., it may have been favored under natural selection in virtue of this design. But that is a distinct matter. What we wish to highlight is that design, in the currently relevant sense, is a present-looking affair—to say that a system has a certain design is to make a claim about its extant features and their contribution to its behavior in the here and now (or in defining the scope of possible designs that could work for a given capacity). The focus on functional principles, rather than reconstruction of evolutionary descent, is explicitly highlighted in some works within systems biology. For instance, Jaeger and Sharpe (2014) state that their aim is not to elucidate particular evolutionary histories but rather to uncover design principles in regulatory networks and to explore why some organizational features work for a defined context and others do not.[8]

Thus, one mode of reasoning that involves design pertains to current role-function. Biologists working in this mode may also believe, for whatever reason, that the current contribution is related, or even identical to, the feature's selected-effect function, but that is not what they are after insofar as they are trying to identify and explain the system's design. This marks one point of difference between our discussion and traditional views of optimality analysis.

4.2. Optimality as a search tool

Another difference has to do with the type of contribution optimality analysis makes. Whenever a theoretical model is constructed, a choice must be made among the possible forms it may take. Sometimes, the range of possible forms is small and constraining the search for the right model is uncomplicated. But often enough, narrowing down the options is a substantial challenge. This holds especially in some mathematical contexts, in which the space of possible models can be (literally) infinite. In this kind of situation, tools that allow one to systematically "close in" on a model are highly valuable. We suggest that optimality as well as other design-related criteria (such as robustness, discussed below) may serve this role. Indeed, optimality can be very powerful in this role, since in many cases there is either a unique or a small number of optimal solutions to a problem.

As we saw above, Itzkovitz et al. are explicit that this is their motivation for applying the tools of optimal control theory. While they had prior indications that crypt development is a fast process, they were not employing the logic of an evolutionary study, in which a trait is presumed to have been optimized by natural selection and optimality analysis is then used in order to elucidate the selection pressures that gave rise to said trait. Rather, the appeal to optimality served them in a purely methodological role, as a search tool, and does not embody presuppositions concerning the role of selection or the adaptedness of the trait under investigation.

It might still be asked whether, absent assumptions about natural selection, an application of the tools of optimality analysis in the manner of Itzkovitz et al., is justified and if so how. In this particular case, Itzkovitz et al. offer some tentative reasons for thinking that crypt maturation occurs very quickly. They argue that fast maturation would be important for the mouse's viability at a young age, and they cite evidence to the effect that crypt cells divide rapidly during development. However, in the end the proof of the pudding is in the eating—conducting the analysis this way yields testable results; and when tested, these results are borne out. Moreover, as we have noted, Itzkovitz et al. state explicitly that crypt development may not be optimal from an evolutionary standpoint, yet they do not see this as invalidating their results, which primarily consist in proposing, and then testing, a certain dynamic cell division pattern.

Thus, we suggest that in this kind of context the appeal to optimality is justified as a methodological stepping stone: while the method of analysis may be interesting and worth highlighting, the results do not depend on it for their validity. The experimental results are what validate the claim that crypt development follows a "bang bang" trajectory, not that this trajectory is in fact optimal.

We have described the role of optimality analysis as methodological in character. We would like to emphasize, however, that it is not a form of methodological or heuristic adaptationism (Godfrey-Smith 2001; Resnik 1997). These terms denote a merely methodological stance one may take *in pursuing explanations that avert to natural selection*. As Godfrey-Smith puts it: "a scientist might find that, as a matter of fact, the most helpful way to proceed is to look for a selective explanation in every case, even if many phenomena are eventually shown to have non-selective origins" (Ibid, p. 342). In contrast, the methodological role played by optimality analysis in the example we have looked at is altogether orthogonal the search for selective (or on-selective) explanations.

4.3. Design-related search tools beyond optimality

To further buttress these points we will briefly look at another instance of the strategy we have in mind, in which the property of *robustness*—a concept that also originates from and has importance in engineering—plays a role parallel to that we have previously seen for optimality.

Robustness, in the presently relevant sense, is the stability of a biological system in the face of perturbations. Robustness has received much theoretical attention in recent years, including an increasing volume of mathematical modeling (Kitano 2004; Alon 2007). Some studies in this area treat it as a phenomenon in and of itself, seeking design principles underlying robustness across different systems (Acar et al. 2010; Shinar and Feinberg 2011). Other work treats robustness not as an explanandum, but rather as a constraint. Specifically, robustness defined in mathematical terms can serve as a criterion for selecting among possible models. As Stelling et al. (2004) ~~contend~~explain, such an approach "relies on the following logic: biological systems are robust—therefore an appropriate mathematical representation must also be robust.

Consequently, mechanistic details that are necessary to satisfy this criterion form testable hypotheses." This strategy parallels the one we discussed above for optimality: one has some initial (typically empirical) indication that the system of interest exhibits a certain "generic" feature—in this case, robustness. Next, one considers the general form of a mathematical model for the phenomenon in question. Typically there is a large class of possible models, so to choose among them one employs the generic property as a selection criterion on the space of models. If such a method yields a restricted set of models that might be operative in a given system, appropriate experiments are performed, testing other, non-generic properties of the models.

A study by Eldar et al. (2002) neatly exemplifies this strategy. These investigators modeled the generation of a bone morphogenetic protein (BMP) gradient, key to early pattern formation in *Drosophila*. In preliminary experiments, they established that the gradient is robust to changes in the concentration of various components of the system. They then considered a large family of possible models, representing different possible architectures for the network of extracellular proteins that are produced, degraded and causally interact through the developmental process. Most of these models showed no significant robustness properties in computer simulations and were excluded from further study. The small number of models that did exhibit a high degree of robustness also had a common design, involving a so-called "shuttling-degradation mechanism" where a reaction- complex mediates diffusion and spatial storage of the morphogenetic protein (Ben-Zvi et al. 2011). Eldar et al. then performed experiments to confirm that a shuttling mechanism is indeed at work. On this basis they suggest that "[a]pplying the same modeling principles to other systems might identify additional 'design principles' that underlie robust patterning… in development." (Ibid, p. 308).

In sum, the appeal to design can play a part in an attempt to single out (potentially generalizable) organizational features of a mechanism. In this endeavor, it is common to come across a search problem: possible designs are numerous, and identifying the mechanism at work on the basis of empirical information is difficult without guiding assumptions on which organizational patterns are possible. Design-inspired properties conceptualized in mathematical terms—earlier optimality, here robustness—are used to narrow down the space of possible designs. This allows the generation of testable hypotheses and (if all

goes well) validation of the model. In this process there is little if any role for evolutionary considerations; the investigation is not aimed at elucidating the system's selective basis.

5. Conclusion

We have identified a novel role for design thinking in contemporary biology, as a heuristic strategy to constrain the search for organizational features. We have argued that this role is not premised on assumptions about adaptation and evolution by natural selection. Role-functional and evolutionary analyses may productively be combined but they need not be—researchers can analyze design without making a commitment as to *why* a particular design exists. Design thinking is directed at identifying generalizable organizational principles that enable systems to exhibit specific capacities. Often, scientists reason about these design principles in the same manner as engineers, or rather reverse engineers, would. Their goal is to demonstrate that certain design principles in fact govern the system they are investigating. Thus, both Itzkovitz et al. and Eldar et al. invoke design considerations to hypothesize that a certain design was operative in the biological mechanism in question and then present evidence that it is. What they did not do was hypothesize and provide evidence concerning the role of natural selection in shaping said design. Rather, they conducted a formal analysis, drawing on mathematical criteria for optimal crypt development and robustness, respectively, as a search tool to narrow down the space of possible mechanisms.

It might be objected that while it is true that the work we have described is not overtly premised on evolutionary considerations, nevertheless the researchers in question presume that biological systems have been shaped extensively by natural selection, and this is what motivates them to invoke optimality and related methods. In reply, we want to clarify that our argument does not concern underlying beliefs or background motivations, but rather the manner in which the use of optimality analysis, robustness and related tools are justified, and the type of information such studies yield. First, as we have seen in the last two cases we have discussed, the appeals to optimality and/or robustness are justified by the results of subsequent empirical investigations that pertain to role-functionality in the here and now. Second, as we have highlighted, the fact that results lead to testable predictions concerning unexpected features of the

extant mechanism allows these studies to be tested independently of evolutionary hypotheses. That said, we do not wish to deny that some, perhaps many, biologists working in these areas do have adaptationist leanings, and may be driven towards such studies on this basis. Indeed, one sometimes finds general or veiled allusions to natural selection in discussion sections and review essays. However, as we hope our discussion shows, and as we think the scientists in question would agree, the content of the work and the information it generates, do not rest upon assumptions or evidence about adaptation and natural selection. Furthermore, while arguing that optimality and robustness play heuristic roles in the discovery of design principles, we have not tried to evaluate the soundness of these strategies. Most heuristics have inherent biases (Wimsatt 2007). But understanding the limitations of research methodologies includes clarifying the implications of particular methodological choices. Our examples show that insofar as adaptationist leanings form a background motivation, this need not filter through and affect the content or justification of the research in question. Therefore, if we want a comprehensive understanding of the place of design thinking in present-day, we need to make room for design sans adaptation.

Acknowledgments

We wish to thank Shalev Itzkovitz for oral discussion and written correspondence as well as two anonymous reviewers for helpful comments. Sara Green gratefully acknowledges support from the Danish Research Council for Independent Research/Humanities for the grant Philosophy of Contemporary Science in Practice.

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[1] An early formulation along similar lines can be found in Lauder (1982, p. 58): "I define design as the organization of biological structure in relation to an hypothesized function." Lauder explicitly distinguishes 'design' from 'adaptation', which "is restricted to features that have arisen by means of natural selection."

[2] Calcott (2014) discusses the role of design thinking in non-adaptationist evolutionary analysis. We are in agreement with much of what Calcott says, but we will not dwell on the connections (and differences) to our paper.

[3] While some researchers have questioned the ability of biological research to identify the design principles actually operative in a given organism (Marom et al. 2009), there are large-scale projects devoted to evaluating the success of procedures for reverse engineering (Stolovitzky et al. 2007). Our concern, however, is not with the potential for success in these projects but with the conceptual implications of this research strategy.

[4] These two facts are linked: part of the interest in this system stems from the (hotly contested) role of stem cells in carcinogenesis.

[5] Nowak et al. regard cancer as a somatic evolutionary process, i.e., as involving natural selection among cells within the body. There is an ongoing discussion both among biologists and in recent philosophy about whether cancer is rightly viewed as form of intra-bodily evolution (Germain 2012). This issue does not affect our argument. To forestall confusion, we will not describe cancer in evolutionary terms.

[6] Itzkovitz et al. offer some (non-evolutionary) support for this. We discuss this aspect below—

see Section 4.2.

[7] Thus, they do not test—nor suggest tests—for an evolutionary hypothesis concerning crypt development.

[8] For further examples, see Shinar and Feinberg (2011).