Design Explanation in Systems Biology and Design Principles

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Abstract

Based on the case of bacterial chemotaxis, Braillard, Green and Jones, and others, present a new kind of explanation – design explanation in systems biology, which is entirely distinct from mechanistic explanation. Design explanation in systems biology is based on laws in biology – design principles, and is intended to answer questions concerning topological structures. In this article, I argue that design explanation fails to establish itself by design principles in systems biology but succeeds in building up itself by laws of physics in physiology, the reason behind is that design principles function differently from laws of physics in design explanation.

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1.Introduction

In recently years, design explanation has been advanced and endorsed by a group of supporters in the context of systems biology. Design explanation aims to answer questions concerning biological structures or designs[[1]](#footnote-1) in biology, like why a specific structure appear in a particular organism. Design explanation is first put forward by Wouters in the context of physiology (Wouters 2007), and then is developed by Braillard (Braillard 2010) and championed by Green and Jones (Green and Jones 2016) in the discipline of systems biology. The supporters of design explanation in systems biology hold the view that design explanation exists in systems biology, and it is also independent from classical mechanistic explanation. In the following, I will say something about the general background of where this new explanation in systems biology may come from.

The Neo mechanistic framework has been dominating philosophical analysis of biology for two decades (Machamer, Darden, and Craver 2000; Glennan 2002; Bechtel and Richardson 2010). Mechanistic explanation is philosophical account of how life scientists attempt to explain various biological phenomena, in terms of their underlying mechanism, among much of biological disciplines, including molecular biology, neuroscience and physiology, etc. The least controversial definition of mechanism, I think, is the minimal definition of mechanism given by Glennan, which is captured by a formulation—a mechanism for a particular phenomenon consists of entities or parts whose activities and interactions are organized so as to be responsible for the phenomenon (Stuart Glennan & Illari, 2017). I will put this version of mechanism as the basis for the discussion relating to mechanism in this paper.

This mechanistic framework has become increasing prevalent in understanding how biological phenomena are explained across a wider range of scientific areas, like biology, cognitive science, psychology, etc (Chemero and Silberstein 2008; Weiskopf 2011; Woodward 2013; Kaplan 2015). This naturally gives rise to the question of to what extent mechanistic framework can be applied in these areas. Besides this question, a set of closely related questions in these domains have been lively debated: whether a competing kind of explanation exists, and if it exists whether it can be incorporated into mechanistic explanations.

Among the debates in these disciplines, the debate in systems biology is a special and interesting one, because systems biology has distinctive features yet shares some similar characteristics from molecular biology. It is natural to wonder that is mechanistic explanation the exclusive type of explanation or does there exist a different kind of explanation in systems biology? The similar side is that the philosophical framework of mechanism is forming by drawing numerous examples mainly from the biological disciplines of molecular biology and neurobiology (Machamer, Darden, and Craver 2000), and systems biology has historical roots in traditional molecular biology (Westerhoff and Palsson 2004). The different side is that a major characteristic of systems biology consists in its large collection of heterogeneous approaches in both experimental and theoretical direction (O’Malley & Dupré, 2005). Put it more specifically, the research methodology in systems biology usually includes theoretical analysis, biological experiments, and computational simulations. As a result, there is no standard and unified definition of “systems biology”. A distinctive feature of systems biology from other biological disciplines like molecular biology exists in its heavy usage of modeling techniques, which draw resources from disciplines like mathematics, computer science, and engineering.

The modeling approaches in systems biology can be categorized into two types: dynamical simulation modeling as a quantitative model and network modeling as a qualitative model (Klipp et al. 2016). Dynamical simulation modeling centers on tracking the dynamical behavior of a system and its parts over time, by using mathematical modeling and computational modeling. Network modeling aims to represent a system’s organizational structure in terms of static network at an abstract high level, by mainly using a mathematical branch – graph theory[[2]](#footnote-2). Systems biology frequently combines either or both of the above two modeling methods with traditional qualitative experiments, whereas traditional biological disciplines like molecular biology mainly rely on experimental techniques to investigate the biological systems. One of the differences that biological network modeling brings – design principle is my only focus in the article, and I will talk about it in more details. These differences lead to my reassessment of how philosophical framework of mechanism can be applied in systems biology, and to my investigation of whether a rival explanation from mechanistic explanation really exists in this area. One of the autonomous explanations they give in systems biology is design explanation, which gives account of why a particular circuit appear in a certain biological system exhibiting a particular function.

In the discussion of whether design explanation exists and its significant basis – design principle in network modeling approach, three widely disparate positions appear. The first camp puts forward a new type of explanation – design explanation, which is based on design principle, and firmly believes that design explanation is independent of mechanistic explanation (Braillard 2010; Green and Jones 2016; Brigandt, Green, and O’Malley 2016). The second camp claims that design principle bears a certain explanatory role in explaining biological phenomena, and that this point is underappreciated (Levy & Bechtel, 2013). The third camp insists that design principle plays no role in explaining and merely facilitates the last two stages of searching for mechanism, namely, constructing and evaluating mechanism schemas (Craver 2007; Matthiessen 2017). Design principle simply serves as a new heuristic strategy in mechanism construction, in addition to traditional heuristic strategies – analogical reasoning, decomposition and localization. I argue against the first camp that design explanation fails to establish itself by design principles in systems biology but succeeds in building up itself by laws of physics in physiology, the reason behind is that design principles function differently from laws of physics in design explanation.

This article is structured as follows. Section 2 introduces a core concept of design principle and provides requisite knowledge about bacterial chemotaxis exhibiting robust perfect adaptation. Section 3 rephrases how Braillard, Green and Jones give a new type of explanation – design explanation within systems biology in the definitive framework of design explanation by Green and Jones. In the bacterial chemotaxis case, Braillard answers the design question – why integral feedback loop rather than other designs appears, by pointing out that integral feedback loop satisfies not only a sufficient but also a necessary condition for robust perfect adaptation. Green and Jones answer the same question by using the design principle of integral feedback loop. Section 4 describes the latest scientific findings about four kinds of topological structures have the ability to realize robust perfect adaptation, which are captured respectively in four design principles. Section 5 first chooses Braillard’s argument for design explanation as the target of analysis because Green and Jones’ argument is itself incomplete to give design explanation, then examines how Braillard’s argument fails in the lights of four design principles, at last compares design explanation in physiology with design explanation in systems biology to find out the deep reason why design explanation based on design principles fails. Section 6 responds to an objection.

2.Preliminary

In order to investigate whether design explanation by design principle exists in systems biology, we need to fully understand the crucial concept involved, and we need to familiar with the case of bacterial chemotaxis because Braillard, Green and Jones give design explanation through this case and I will take it also as the basis of my discussion.

2.1Design principles

It is significant to clarify the notion of design principle, because design principle plays a crucial role in design explanation in systems biology. Design principles are defined by a systems biologist as “the rules that underlie what networks can achieve particular biological functions” (Ma et al. 2009, 760). Design principles are defined by a philosopher as “identify formal rules about what organizational structure can achieve particular types of biological function” (Green 2015, 17). These two definitions show no fundamental differences, thus design principles in general aim to find out the design rules that what kinds of organizational structures can perform what kinds of function.

I will describe a typical approach to discover design principle and special features of design principle to illustrate this conception. Systems biology arise partly because the need to investigate of the vast amount of high throughput biological data. In order to analyse and make sense of these data, biological network analysis emerges. Network analysis is a tool to study biological systems with the help of mathematics, especially graph theory. Graph theory is used to model complex biological systems or subsystems by representing them in the form of graphs. Each graph is a mathematical object composed of a series of nodes, which represent biological components and activities, and connecting links, which stand for the interactions. Formally, a graph G = (N, E) consists of a collection of nodes N and a collection of edges E, where each edge is associated to two nodes.

Networks analysis overlooks all the systems’ details and simply represents them as networks. Network emphasizes structures of the network otherwise would remain unnoticed. The purpose of network analysis is to discover network properties in order to distinguish between different types of networks. A common tool to analyse, simulate, and visualize the biological system is the algorithm in graph theory. As a result, many interesting properties of molecular networks haven been discovered by analysing large-scale molecular networks and inducing general information regarding their structure and functional consequences. Most noticeably results are small world organisation, scale-free networks, modularity, network motifs, and so on.

Among these results of network analysis, network motifs serve as the foundation of design principles. These motifs were discovered as recurrent regulatory patterns from statistical analysis of certain subgraphs frequencies in the graphs representing transcription networks. Uri Alon first argues that network motifs exist and they correspond to general design principles. “Our goal will be to define understandable patterns of connections that serve as building blocks of the networks. Ideally, we would like to understand the dynamics of the entire network based on the dynamics of the individual building blocks” (Alon 2007, 27) After that, a substantial number of studies have been investigated network motifs and their potential functions. As a result, some structures, or circuits, or modules are commonly found and correspond to general solutions to functional problems (Tyson, Chen, and Novak 2003; Ma et al. 2009; Novák and Tyson 2008; Tyson and Novák 2010; Ferrell 2016).

Eight types of networks which carry specific biological functions are common in transcription regulation and signalling networks. They are autoregulation, cascades, positive-feedback loops, feedforward loops, single-input module, negative-feedback loops, integrated FFLs, and integrated motifs and dense overlapping regulations (Shoval and Alon 2010). These networks correspond to different design principles respectively. For example, the feed-forward loop motif was shown to have particular information filtering capabilities within the process of gene regulation. All of the network motifs can be diagrammatical presented by graph theory. For example, one of these subcircuits – negative feedback loops can be represented as a directed graph, consisting of three nodes u, v, m and three edges. The search for general design principle is the opposite of studies that are based on evolutionary contingency[[3]](#footnote-3), according to a leading hypothesis, because the biological network motifs are independently selected by evolutionary processes in a converging manner[[4]](#footnote-4) for their functional or structural properties.

As in our case, three heterogeneous approaches are used to find plausible structures for robust perfect adaptation (Araujo and Liotta 2018) and their corresponding design principles. The first approach is to model the well-studied biological systems which exhibiting robust perfect adaptation. The abovementioned model of bacterial chemotaxis by Barkai and Leibler is a paradigm for this approach. The second approach is to devise modifications to input-output network circuits and find out what designs will achieve robust perfect adaptation. Tyson, Chen, and Novak’s discovery of sniffer circuit that shows perfect adaptation is of a great example. (Tyson, Chen, and Novak 2003). The third approach is to search network circuits with two to three nodes by high-throughput computation. As it is shown in Ma’s paper, only two kinds of network motifs that are capable of performing robust perfect adaptation (Ma et al. 2009).

2.2 The case of bacterial chemotaxis

The case of bacterial chemotaxis under discussion is from an organism called *Escherichia coli*. Bacterial chemotaxis behavior appears in many bacterial species, and the corresponding protein signaling pathways are the underlying mechanisms responsible for this phenomenon. The reason why the example of *Escherichia coli* is chosen is because its particular signaling pathway is one of the most well-understood mechanism and is also relatively simple, compared to other pathways for bacterial chemotaxis behavior. Thus, this least controversy example is legitimate to serve as a foundation for discussion.

What are the behaviors and unique properties of bacterial chemotaxis? It is the movement of an organism in response to a sense of gradients change in chemical stimulus, moving towards attractants and moving away from repellents. Bacterial chemotaxis owns a unique property – robustness perfect adaptation. *Adaptation* refers to the bacteria’s ability to return to the normal steady-state tumbling frequency, after changes in the tumbling frequency that is the system’s first response to sensing the external concentration gradient. *Perfection adaptation* means that the bacteria is able to return to the steady-state tumbling frequency at the exact same level after its responses to the concentration gradient. As a result, the steady-state tumbling frequency is independent on the levels of chemical concentration. *Robustness perfect adaptation* is an updated version of perfection adaptation, and it means that the system is robust to some of the variations of parameters and remains its normal function, regardless of the changes of certain parameters’ values.

The robustness perfect adaptation property of bacteria chemotaxis can be fully understood by its mechanistic model of signaling pathways. This chemotaxis mechanism is generally comprised of two pathways. One pathway diagrammed in left part of figure XXX is responsible for responding to external chemical stimulus. Attractants and repellents molecules from external environment firstly bind receptors, which are specialized detector proteins that pass through the inner membrane. The state of receptors determines the states of CheA that is bound to each receptor. When the receptor binds to attractants, the activity of CheA become inactive. Inactive CheA reduces the rate of phosphorylation to CheY, thus the number of CheY-P decreases.

The second pathway of the chemotaxis mechanism diagrammed in right part of figure XXX contributes to the adaptation. The adaptation is achieved by a special pathway of the system. Each receptor has several methylation sites to each of which a methyl group (CH3) is added. Methylation of each receptor increase the activity of it, thus enhancing the activity of CheA. Methylation of the receptor is catalysed by an enzyme -CheR at a constant rate regardless of the binding states of the receptor. Methylation of the receptor, however, can also be removed by another enzyme – CheB-P, the amount of which is determined by the activity level of CheA. Binding to attractants turns the CheA into inactive state, leading to the reduced amount of CheB-P. A fewer number of CheB-P bring about the decreasing remove of methylation on the receptor. Thus, the total number of the methylation increases, which in the end reactivate the decreased performance of the CheA. The same is true when the receptor is bind to the repellents: the initial activation of CheA is decreased or balanced by the lively deactivation by CheB-P. Thus, the product of CheA counteracts itself regardless of adding attractants or repellent. The negative feedback loop from CheA through CheB-P to receptor plays a necessary and significant role for perfect adaptation in this case.

3.How design explanations are given in systems biology

Braillard, Green and Jones both claim that design explanation is a new kind of autonomy explanation in systems biology besides the mechanistic explanation.

Design explanation gives account of why a particular circuit appears in a certain biological system exhibiting a particular function. The concept of design explanation is firstly put forward by Wouters in the discipline of physiology on a high level, and then this conception is borrowed by Braillard and is further clarified by Green and Jones within the area of systems biology on a lower molecular level. In this section, I will describe and analyse how Braillard, Green and Jones give design explanations in systems biology, by rephrasing their arguments in Green and Jones’ framework of design explanations.

Green and Jones’ framework explicitly identifies general key components of all design explanations in biology for the first time (Green and Jones 2016), and I will use this framework to rephrase Braillard, Green and Jones’ arguments in this section to explicate how they give design explanations step by step. One point worth our attention is that although Green and Jones’ came up with this definition framework of design explanation, they didn’t apply this framework in describing how design explanations are given in systems biology in the same paper. The reason why I choose this framework as the foundation for our discussion is that it logically decomposes design explanation into smaller components, which is beneficial to our careful examination.

The definition framework of design explanation by Green and Jones is as follows.

“1. A claim that organisms within some class C, differing with respect to certain biological details, share certain trait or ‘design’ T with functional property P.

2. A demonstration that certain invariant generalizations, principles and other

formal constraints F limit the scope of possible designs for C-type organisms

exhibiting P.

3. An inference that there are formal dependency relations between T and P[[5]](#footnote-5),

such that having T is better for an organism’ s in C exhibiting P than is

having alternative traits Z1, …, Zn, regardless of differences of biological

detail among members of C.” (Green and Jones 2016, 365)

These three necessary components determine whether design explanation exist or not. That is, if what so called design explanation has these three components, then design explanation exist; if what so called design explanation lacks any one of these three components, then design explanation fail to exist. If design explanation exists, I will add another requirement to further investigate the explanatory autonomy of design explanations. This new requirement determines whether design explanations are genuine autonomous explanations and are independent of causal explanations.

4. A comparison that design explanations can’t be reduced to causal explanations, which is done by comparing the key features of causal explanations and the design explanations.

These four conditions serve as the foundation of the following discussion, and I will refer them in the later as the claim of condition (1), the demonstration of condition (2), the inference of condition (3), and the comparison of condition (4). Through the case of bacterial chemotaxis, Braillard, Green and Jones claim that not all explanations in systems biology fall into the category of mechanistic explanation, there exists a new type of design explanation, which is a completely independent explanation. In the definitive framework of design explanation by Green and Jones, I will reframe how Braillard, Green and Jones advanced design explanation within systems biology bit by bit. In general, their arguments can be rephrased into the following four conditions.

(1) A claim that organisms within some class C, differing with respect to certain biological details, share the same design T– negative feedback loop with functional property P – robust perfect adaptation.

(2) A demonstration that the design principle of integral feedback loop by Green and Jones or the invariant generalization that integral control is sufficient and necessary to robust perfect adaptation by Braillard limits the scope of possible designs for C-type organisms exhibiting P – robust perfect adaptation.

(3) An inference that there are formal dependency relations between negative feedback loop and robust perfect adaptation, such that having T – negative feedback loop is better for an organism’ s in C exhibiting P – robust perfect adaptation than is having alternative designs Z1, …, Zn, regardless of differences of biological detail among members of C.”

(4) A comparison that this design explanation can’t be reduced to causal explanation, which is done by comparing the key features of causal explanation and design explanation.

I will describe in details how Braillard, Green and Jones give their arguments in the above four conditions. In regard to (1), Barkai and Leibler begins with the causal details of these signal transduction pathways, which includes the specific components, how they interact with each other, and how they are organized in the form of networks. Then, they model the dynamics of bacterial chemotaxis’ mechanism in terms of differential equations. At last, their model explains why this mechanism is able to produce robust perfect adaptation. Barkai and Leibler’s model first point outs that there exists an organism, which share the same topological circuit – negative feedback loop, and the functional trait – robust perfection adaptation.

In regard to (2), by first rearranging Barkai and Leibler’s equations in their model through the previous equations of integral feedback control, and then simplifying the rearranged equations, Yi’s team at last obtain the same equation and result in the Barkai and Leibler model. That is, Yi attempted to associate the principle of integral feedback control[[6]](#footnote-6) with an instantiation of negative feedback circuit which is a recurrent network motif. Tau-Mu Yi proved that the negative feedback loop in this case instantiates and accords with the principle of integral feedback control through theoretical analysis, and that the level of methylation activity functions as the integrator[[7]](#footnote-7) (Yi et al. 2000). As a result, Yi’s team demonstrated that the integral feedback control is a built-in structure in robust perfect adaptation, and that integral feedback control is not only sufficient but also necessary for robust perfect adaptation.

Based on the findings of Tau-Mu Yi’s group, especially their statement that ‘Furthermore, and this is crucial, [the researchers] claim that integral feedback control is not only sufficient but also necessary for robust perfect adaptation’, Braillard will say that the invariant generalization that the integral feedback control is sufficient and necessary to robust perfect adaptation limits the scope of possible designs for C-type organisms exhibiting P – robust perfect adaptation.

Green and Jones takes one step further and connects the idea that integral feedback control is sufficient and necessary to robust perfect adaptation with the design principle of integral feedback control. Based on Yi’s finding that even though the specific model may change, the integral feedback control is still sufficient and necessary for robust perfect adaptation, they claim that “Placing the Barkai-Leibler model in the general framework of control engineering reveals that the design principle – integral feedback control … serves as a formal constraint on any model of a system displaying robust perfect adaptation”. Thus, the design principle of integral feedback control limits the scope of possible designs for C-type organisms exhibiting P – robust perfect adaptation.

In regards to (3), the design principle of integral feedback control, or the invariant generalization that the integral feedback control is sufficient and necessary to robust perfect adaptation, determines the functional dependency between the topological structure – negative feedback loop and the functional trait – robust perfection adaptation. Thus, the functional dependency between the negative feedback loop and the function of robustness perfect adaptation is established, giving account of a certain biological circuit's appearance, or explaining why the mechanism is organized in this way rather than any other ways. In short, the above three steps build up the design explanation, which answers the question why this topological structure is negative feedback loop rather than other hypothetical structures like positive feedforward loop or others in this case.

In point to (4), design explanations are also distinctive from and irreducible to a kind of causal explanation – mechanistic explanation. Mechanistic explanations focus on the causal process operating in time and space. A minimal definition on mechanism captured common basic assumptions of different strands of definition on mechanism: “A mechanism for a phenomenon consists of entities (or parts) whose activities and interactions are organized so as to be responsible for the phenomenon (Glennan and Illari 2017).”

Mechanisms are composed of organized set of entities and activities. While design explanations in systems biology are simply point out why a certain biological module appear and why this specific biological circuit, performing a particular function, is structured in this way rather than other fictitious ways. A detailed mechanistic model can explain many causal aspects of the phenomenon, but it can’t explain why a certain structure is present which involves non-temporal relations and constraints. The relation between functional constraints and the structure is a non-causal one that doesn’t occur in space and time. Design explanations focus on the non-causal dependence between the functional constraints and the general organizational features.

The pivotal distinction between design explanation and mechanistic explanation here is that the former answers the question begins with why and the later tackles the question begins with how. Design explanation is a kind of non-causal explanation which gives account of explanation not in terms of cause or mechanism but in terms of constraint. This non-causal explanation answers why questions not what or how questions which involves the actual process and cause for targeted phenomena. In contrast, mechanistic explanation address what and how questions in terms of the arrangement of the entities and their activities for specific phenomenon. A failure to distinguish different types of explanations can lead to a misunderstanding of design explanations.

Through these four steps, Braillard, Green and Jones establish a new kind of autonomous explanation, design explanation, in field of systems biology based on the above chemotaxis case, and he explicitly contended that design explanation is a competing and independent explanation from mechanistic view of explanation.

4. Recent scientific findings surrounding design explanations in systems biology

In this section, I will look at how three other design principles can perform the function of robust perfection adaptation. The second class of network circuit architecture, incoherent feedforward loop with a proportioner node (IFFLP), can also achieve perfect adaptation besides NFBLB topology (Ma et al. 2009). This is the result of independent ground-breaking study by Wenzhe Ma’s group. As pointed out before, Barkai and Leibler’s model and Yi’s team’s theoretical findings belong to one of three heterogenous approaches to find out the possible structures and corresponding design principles for robustness perfect adaptation. Their studies rest on the model of the well-studied biological systems that exhibiting robust perfect adaptation. Ma’s group’s line of research, in contrast, belongs to another approach rather than Barkai, Leibler, and Yi’s approach in three heterogenous approaches. This approach is to search network circuits with two to three nodes by high-throughput computation, and only two kinds of network motifs that are capable of performing robust perfect adaptation – negative feedback loop with a buffering node and incoherent feedforward loop with a proportioner node.

In IFFLP topology, the output node C receives two opposite signals from node A and node B, either of which functions as the proportioner node. Only two particular three-node incoherent feedforward networks can perform perfect adaptation, according to the result of computational simulations for all possible three-node networks. These three-node networks can be represented by graph theory as graph G4, G5. Graph G4 can be presented with vertex set N1 = {a, b, c}, edge set E1= {(a, b), (b, c), (a, c)} and corresponding edge types (", ", :). Graph G5 can be presented with vertex set N2 = {a, b, c}, edge set E2= {(a, b), (b, c), (a, c)} and corresponding edge types (", :, ") .

The design principle of IFFLP points out not only point outs IFFLP topology requirement but also the conditions to perform robustness perfect adaptation: (1) the kinetics of the activation on node C is faster than the kinetics of the inactivation on node C, (2) the activation of node B by the input is operating at saturation and the inactivation of node B by inactivase is operating far from saturation, and (3) the parameters of the system have to be such that node C and node B is synthesized and degraded rather than activated and inactivated. The first condition guarantees that the system exhibits adaptation, because the activation of node C first rise and then fall in this condition. The second condition ensures that the adaptation is perfect or near-perfect, because the saturated activation of node B enables the activation of node C rise and fall back to the pre-stimulus level. The third conditions make sure that perfect adaptation is robust to random parameters.

As a result, Ma’s group identified a kind of organizational structure – IFFLP topology and specified the circumstances requirement for it to achieve a particular biological function. As design principles are defined as the rules that underlie what network can achieve particular biological functions, a general design principle of IFFLP is found out by Ma’s group.

A third kind of design that is able to perform perfect adaptation is state-dependent inactivation, besides NFBLB and IFFLP motifs. The model of state-dependent inactivation is developed with Friedlander and Brenner. This approach is fundamentally different from the previous approach given by Ma’s group or approach given by Barkai and Leibler and Yi’s team. This approach is to devise modifications to input-output network circuits and find out what designs will achieve robust perfect adaptation. This relative simply design principle is inspired by the mechanism of the voltage-dependent sodium channel. This voltage-dependent sodium channel is first activated by depolarization, then become automatically inactivated, and slowly returns to the initial state which is responsive to the next depolarization.

In this model, the node A with three modes receive an input and then give an output. In the first mode – off state, the node A is ready to receive the stimulus. When the node A in off state is subject to stimulus, it automatically turns into the second mode – on state and at the same time generates the output. After producing the output, the node A turn into the third mode- inactivated state which the node A is insensitive to any stimulus. The property of inactivation is either inherent in the system or is regulated by the constitutively active factor in the downstream.

This model of state-dependent inactivation exhibits perfect adaptation as long as the following requirements are met. The requirements are that the transition time from inactivated state to off state is relatively longer than the transition time from off state to inactivated state, that the mass action kinetics of activation and inactivation process are presumed to be simply. This perfect adaptation can be robust in the requirements that the rate of activation process is 0 when A off =0 and greater than 0 in other situations, that the rate of inactivation process is 0 when A on =o and greater than 0 in other situations.

The fourth design principle that can achieve robust perfect adaptation is antithetical integral feedback. Brait, Gupta and Khammash come up with this design principle to enhance the performance of NFBLB topology. The NFBLB topology only presents robust perfect adaptation within a limited range of parameters and if the set points are changed, the whole function of robust perfect adaptation is significantly impaired. They design a new model in gene expression which performs robust perfect adaptation within a broader range of parameters compared to the design principle of NFBLB topology.

This mechanism begins with a gene transcribing into mRNA A by a transcription protein D, and then a transcription protein B that is translated by mRNA A transcripts a transcription protein C – a repressor. This transcription repressor C binds with a transcription protein D stoichiometrically and inhibits it. An integral feedback loop is instantiated in this mechanism. Under the mass action kinetics, this model can be captured by four ordinary differential equations with six kinetic parameters.

Compared to design principle of NFBLB topology within a limited range, this antithetical integral feedback is robust with respect to variation in four kinetics of the systems. That is, the function of robust perfect adaptation in this system remains steady with any variation in one of the four kinetic parameters. The rest two kinetics parameters determine the set point of the system.

As I proved above, the design principle of integral feedback loop is not the only option for performing robust perfect adaptation. In the next section, I will analyze the philosophical implications of this case study on the explanatory status of design explanation in systems biology, thereby determining whether design explanations exist in systems biology.

5.My analysis on the given design explanations in systems biology

In section three, I reconstructed Braillard, Green and Jones’ arguments in the definition framework of design explanation. First, I will demonstrate that Green and Jones’ argument is problematic in itself, and I will choose Braillard’s argument as the basis of my critical analysis. Second, I will carefully examine where Braillard’s argument goes wrong one step at a time, and I argue that there is no such explanation as a design explanation in systems biology. The reason is that there is no functional dependency between the topological structure – negative feedback loop and the functional trait – robust perfection adaptation, which is the crucial element to demonstrate that design explanation is an independent explanation. And I will demonstrate how this functional dependency collapses from the strong evidences of four design principles showed in the last section. Third, I will compare design explanation by design principle in systems biology and design explanation by laws of physics in physiology.

5.1The target version of design explanation for my analysis

As I showed before, there are two ways to demonstrate the autonomy of design explanation: one is from Braillard’s argument, and another one is from Green and Jones’s argument. In the definitive framework of design explanation, Green and Jones’ approach only differs from Braillard’s approach in understanding the concept of formal constraint. In case of bacteria chemotaxis, while Green and Jones understand the formal constraint by design principle of integral feedback control, Braillard understand the formal constraint by invariant generalization that integral feedback control is sufficient and necessary to robust perfect adaptation. In the definitive framework of design explanation, Green and Jones’ way of understanding formal constraint fail to build up a new kind of design explanation, because their understanding can’t establish the functional dependency between certain topologies and particular functions.

Green and Jones’ firstly suggest that Yi’s group finds out the design principle of integral feedback control by placing the Barkai-Leibler model in the general framework of control engineering, and then they take this design principle as a formal constraint that affords and limits the possible designs of C-type organisms. In this view of formal constraint, however, the supposed functional dependency can’t be achieved. In Green and Jone’s own definition of design principle, it involves formal rules that underlie what networks can achieve particular biological functions. From this definition, what we are certain about is that from the specific organizations and certain formal rules, we will know the corresponding functions. In this case, the design principle of integral feedback control merely tells us that the topological structure of negative feedback loop has the capability to exhibit robust perfect adaptation under a series of mechanistic assumptions. Put it simply, the design principle of integral feedback control indicates that the integral feedback control is sufficient to robust perfect adaptation. However, what we are uncertain about is whether negative feedback loop is the only topology or is necessary to robust perfect adaptation. The design principle of negative feedback loop itself doesn’t necessarily mean that negative feedback loop is the only structure or is necessary to achieve robust perfect adaptation. The design principle of negative feedback loop itself is unable to exclude the possibilities that other topological structures are also able to achieve robust perfect adaptation.

In the definitive framework of design principle, this is how Green and Jones understand the demonstration of condition (2): given the type of organisms N, the design principle of integral feedback control, which functions as a formal constraint, sets the limitation and affordance of the possible design. Based on the condition (2), Green and Jones make the inference in the inference of condition (3). However, I argue that inference itself is illegitimate. That is, their understanding of condition (2) can’t directly infer the supposed condition (3) that a formal dependency relation between negative feedback loop and robust perfect adaptation exists in the type of organisms N. To be more specific, the condition (3) can be stated that the particular function of robust perfect adaptation is dependent on the specific topology of negative feedback loop. The definition of dependence relation can be stated as: one kind of entities A is dependent on second kind of entities B, it means that the existence of second kind of entities B is necessary to the existence of one kind of entities A. According to this definition, another way to put condition (3) is that integral feedback control is necessary to robust perfect adaptation. Condition (3) can’t be understood as the other way around: the specific topology of negative feedback loop is dependent on the particular function of robust perfect adaptation, or robust perfect adaptation is necessary to negative feedback loop. The reason behind is that the aim of design explanation is to explain why this actual particular design appears rather than other conceivable designs. This question can be answered by that integral feedback control is necessary to robust perfect adaptation.

If we adopt Green and Jones’ claim that the design principle of integral feedback control sets as the formal constraint for robust perfect adaptation, then the inference that formal dependency relations between negative feedback loop and robust perfect adaptation is hard to achieve. The design principle of integral feedback control only indicates that the integral feedback control is sufficient to robust perfect adaptation, while condition (3) needs to be integral feedback control is necessary to robust perfect adaptation. In order to make this inference sound, an additional requirement is needed – integral feedback control is necessary to robust perfect adaptation. Only under this additional premise that integral feedback control is necessary to robust perfect adaptation, we can deduce that the functional dependency exist between the negative feedback loop and the function of robustness perfect adaptation from condition (2). A point worthy noting is that finding the design principle of integral feedback control is the first step to prove that the integral feedback control is not only sufficient but also necessary to robust perfect adaptation; The second step is to prove the design principle of integral feedback control is the only design principle to achieve robust perfect adaptation. As a result, Green and Jones’ argument is unsound in the definitive framework of design explanation, and their argument alone can’t give a new type of explanation – design explanation.

The invariant generalization by Braillard, in contrast, includes that the integral feedback control is not only sufficient, but also necessary to robust perfect adaptation. According to Braillard’s argument, this invariant generalization is supposed to be the formal constraint limits the scope of possible designs for C-type organisms. As I proved before, this generalization is able to establish the formal dependency between negative feedback loop and robust perfect adaptation. Thus, Braillard’s argument is able to give design explanation, according to the definitive framework of design explanation. We should take the invariant generalization by Braillard rather than the design principle of integral feedback control as the formal constraint for possible designs. In the next, I will take Braillard’s argument as the foundation of my discussion.

5.2 How design explanation fails to be established in Systems biology

My core reason to reject Braillard’s argument is that a supposed formal dependency relation doesn't exist in the types of organisms performing robust perfect adaptation, because four kinds of design principles (integral feedback control, incoherent feedback loop, state-dependent inactivation, antithetical feedback control) can realize robustness perfect adaptation. Without this functional dependency, the question why this type of organisms is better having a negative feedback loop rather than having other conceivable designs can’t be answered. Thus, the design explanation doesn’t exist in systems biology.

As I showed in the last section, the design principle of integral feedback control is not the only design principle that can perform the same function – robust perfect adaptation. Apart from this design principle, three other design principles have the same ability to achieve robustness perfect adaptation: they are design principle of incoherent feedback loop, design principle of state-dependent inactivation, and design principle of antithetical feedback control. These four kinds of design principles (integral feedback control, incoherent feedback loop, state-dependent inactivation, antithetical feedback control) are equally capable of achieving the same function – robust perfect adaptation. It means that design principle of integral feedback control is not the only viable approach to realize robust perfect adaptation. Each of the network circuits can substitute each other under a different set of constraints to display the same function – robust perfect adaptation.

The reason why other design principles exist for robust perfect adaptation is that how biological systems perform robust perfect adaptation in reality doesn’t have to correspond entirely to fundamental control strategies in control theory.

The engineering principle of integral control as a control system[[8]](#footnote-8) attempts to solve the problem that the output of the system must track its desired value regardless of the variations in the internal parameters and the input value. This is done through feeding back the integrated difference in time between the actual output and the desired steady-state output to the system. The whole integral control process can be illustrated in the diagram below. The relations among different variables in the integral feedback control system can be described by a set of equations.

The distinct feature of integral control can be represented as the integral control equation x=y. The equation y=y1-y0 means that the normalized system output Y equals the difference between the actual output y1 and the steady-state output y0 as the normalized system output. The equation y=/x means that the system error x equals the time integral of y. The equation y1=k(u-x) means that the actual output y1 is the product of the difference between the input u and feedback x through k process. Through the integral control, the system will eventually lead to the desired steady-state output as the error gradually approaches 0 via the controlling process.

In control theory, the engineering principle of integral control is achieved through a feedback loop. Once this negative feedback motif is connected with the principle of integral control, the design principle of integral feedback control is identified, for it specifies organizational rules that underlie what networks can achieve particular biological functions. Negative feedback loop can realize the function of robustness perfect adaptation under four mechanistic assumptions[[9]](#footnote-9) of Barkai and Leibler model.

Take, for instance, the integral feedback control instantiated in thermostat. The thermostat can remain the desired temperature in face of the constant external disturbances and internal changes. The integral controller within the system first integrates the difference between the room temperature and the desired temperature, and then feedback the calculated integral difference to the system. Through the iteration of the whole process, the difference ultimately reaches zero and the system remains the desired temperature in spite of constant disturbance.

The u represents the input and k represents the course in which the input u is processed to generate the actual output y1. Given y0 is defined as the steady-state output, Y is denoted as the difference between y1 and y0 as the normalized system output. The system error x, which represents the time integral of y, feedback to the system.

Yi and his colleagues’ claim that integral control through a negative feedback loop is necessary to robust perfect adaptation is based on the comparison between the fundamental control strategies in control theory, which includes PID feedback control, feedforward control, ratio control, cascade control, etc. Any of other common control strategies can’t perform robust perfect adaptation, thus Yi and his colleagues made the conclusion that integral feedback control is necessary to robust perfect adaptation. To be more precisely, their claim that integral feedback control is not only sufficient but also necessary to robust perfect adaptation should be restated into that integral feedback control is not only sufficient but also the only possible strategy in control theory to robust perfect adaptation.

Another crucial step to establish the functional dependency between the negative feedback loop and the function of robust perfect adaptation, is to demonstrate that the design principle of integral feedback control is necessary to give account of the system’s robustness of perfect adaptation. Yi and his colleagues proved that robust perfect adaptation can’t be realized by other control types in control theory, like the proportional control which feedbacks to the system by a linear proportional of the system error. Thus, integral feedback control is the only control type in control theory that can achieve this function.

Yi and his colleagues only exclude other control strategies that may instantiated in biological systems. Constraining only to basic control strategies, however, leaves room for discoveries in other possible biological strategies. In our case, these possible biological strategies contain incoherent feedforward loop, state-dependent inactivation, and antithetical feedback control, which don’t correspond to any fundamental control strategies in control theory. For example, the design principle of incoherent feedforward loop involves a different kind of topology – incoherent feedforward loop from negative feedback loop. From the perspective of topological structure, control strategies in control theory involving feedforward loop is the engineering principle of feedforward control, although the feedforward loop includes but not confines to incoherent feedforward loop. In a feed-forward system, the control variable adjustment is not error-based. Instead, it is based on knowledge about the process in the form of a mathematical model of the process and knowledge about or measurements of the process disturbances. Nonetheless, the design principle of incoherent feedforward loop doesn’t correspond to the engineering principle of feedforward control, although they have similarity in topological structure.

Although the design principle of incoherent feedforward loop is exemplified the engineering principle of integral control (reference), it doesn’t correspond to the fundamental control strategy of integral feedback control. This basic control strategy involves a topological structure of negative feedback loop, whereas the design principle of incoherent feedforward loop involves a topological structure of incoherent feedforward loop.

Biological vs control strategy!

According to the definition of dependency relation, the supposed functional dependency relation between the negative feedback loop and the function of robustness perfect adaptation fails to exist. If there is an autonomous explanation – design explanation, then it must satisfactorily answer the question that why does negative feedback loop rather than other possible topological circuits appear in robust perfect adaptation. Eventually, design explanation is a non-existence in systems biology. As a result, we can’t explain why this type of organisms is better having a negative feedback loop rather than having other conceivable designs, like incoherent feedback loop or state-dependent inactivation or antithetical feedback control. These four kinds of topological structure, including negative feedback loop, have the equally ability to realize robust perfect adaptation.

5.3 Comparison with genuine design explanation in Physiology

Braillard clearly points out that his using of term “design explanation” is adopted from Wouters. Their usage of design explanation concept shares some similarities and yet some differences. Understanding usage differences help us determining the explanatory role design explanation plays in systems biology. In particular, the notion of design explanation in systems biology involves the idea of design principle, which is lack in the context of physiology.

In point to (1), design explanations in physiology first point out that there exists a group of organisms, which share the same internal, external circumstances, and a respiration design. For example, there exists a class of animals, which all live on earth, exceed a certain level of size and activity, and share the same respiration design – having a specialized respiration organ rather than respiration through the whole body’s surface.

In point to (2), given the organism’s internal and external circumstances, the same respiration design can be deduced from a set of laws of nature. It is laws of nature that limit and afford the respiration design, provided the organism’s internal and external circumstances. For instance, why the respiratory face of organisms has to be this design – thin, large and permeable? The internal circumstance is that the organisms exceed a certain level of size and activity, and the external circumstance is that the organisms live on earth. Given the organisms’ overall circumstances, the respiratory design – thin, large and permeable can be deduced from laws of nature – Fick’s law. To be more specific, the overall circumstance is the organism’s need for a high level of oxygen; Fick’s law[[10]](#footnote-10), a law of physical chemistry, states that the rate of diffusion of a gas is proportional to the surface area available for diffusion, the concentration gradient over the distance, the diffusion coeffecient and is disproportional to the distance of diffusion. According to Fick’s law, the rate of diffusion of a gas must be large enough for the need for a high level of oxygen, then the surface area available for diffusion must be large enough, the material for diffusion must be permeable (high diffusion coeffecient) and the distance across for diffusion must be small. As a logical result, the respiratory surface’s design must be thin, large and permeable.

In point to (3), design explanation gives account of why a certain organism have a certain trait rather than any other possible traits. That is, in a given circumstance, it explicates why the actual design of a certain trait is better than alternative hypothetical designs. Design explanations are able to not only answer broad questions concerning structures or designs like why tetrapods respire through lung instead of gills, but also more specific organizational questions like why fish’s respiration organ is more minutely divided than tetrapod vertebrates’ respiration organ. The question is answered by specifying the functional dependence between this trait and other traits, which is determined by the laws of physics. As shown in second condition, the laws of nature determine the functional dependence between the organism’s circumstances and its trait design. For example, the relationship between the trait of having lung and another trait of living on land is functional dependence, which is determined by laws of nature including Fick’s law. Other explaining traits and its environment set the constraints on what can be alive, which means why the real design of a trait is needed than any others are due to its conformity to these constraints. That is, if an organism has certain traits, it can't be alive if the trait to be explained is substituted by a specific hypothetical one. For example, if an organism living on land, it must have lung rather than gills because if this organism living on land has gills it can’t be alive.

In point to (4), design explanation seems like a kind of causal explanation – function explanation, but in fact it can’t be identified and reduced to function explanation. Functional explanations explicate why the trait is present by the effect of the trait's presence which can be traced back to how this trait's being selected in the past by selected effect theories (reference) or how this trait contributes to the working of the complex system by systemic theories(reference). In selected effect theories, functional explanations appeal to the fitness differences among a certain trait's variants that actually exist and resort to what happened in the past, while design explanations are contrastive and point out the synchronic relation between the organism's different traits. In systemic theories, functional explanations specify the underlying causal mechanism of a certain capacity and how this capacity that performs specific biological role is brought about by the organized activities of that system's parts, while design explanations tell why this biological role is performed this way rather than other conceivable ways.

A noteworthy point is that Wouters said little about the relationship between design explanation and mechanistic explanation. But he suggested that if design explanations are given within a mechanistic perspective, it gives account of why a certain trait is required in the context of the overall design of a living mechanism (in the conditions) and reveals the constraints imposed on what mechanism can be alive and what mechanism can’t be alive. It is neither an evolutionary explanation nor a functional explanation.

In general, establishing the functional dependency relations is crucial to design explanations both in physiology and systems biology. The functional dependency in physiology is solid, because it is established from the laws of nature. In contrast, the reason why the functional dependency fails to exist in systems biology is because that the topological structures do not necessarily determine the function, vice versa. Normally, the general design explanations tell us what kinds of topological structures under what circumstances can achieve what kinds of functions, but it fails to guarantee that a topological structure is necessary for a particular function to operate.

A comparison to design explanations in physiology made by Wouters can help us better understand why design explanations in systems biology given by Braillard fail. In physiology, it is the general physical theory - Fick’s law that determine the dependence of the organism’s environment and its trait design. In other words, given the organism’s internal and external circumstances, its trait design can be deduced from the law of physics. Take, for instance, given the way organism's inhale of oxygen, the design of the respiratory surface can be deduced by Fick’s law in the form of mathematical equations. Fick’s law establishes the dependence between organism's inhale of oxygen and the respiratory surface.

In systems biology, however, design principle is hard to establish the dependence between a topological structure and a function property. The finding process of design principles commonly starts from the topological structures, and then finds out under what circumstances can these structures achieve the particular functions. In our case, four kinds of design principles exist for robust perfect adaptation, but none of design principles is necessary to this function. The relation between function property and topological structure in our case is not ideally one to one correspondence, but is many to one correspondence. As a result, the functional dependency between a certain topological structure and the function of robustness perfect adaptation is a non-existence.

The reason why topological structures do not necessarily determine the function is that under different ranges of parameters, a certain topological structure can exhibit a wide range of dynamical behaviours. In other words, the topological structure alone is insufficient to determine its function. For example, negative feedback loops can both exhibit damped oscillation behaviour and robust perfect adaptation under different parameter configurations. A point worth noting is that some topological structures only correspondent to a certain function regardless of parameters choices. Yet, some topological structures only correspondent to multiply functions under different ranges of parameters. The reason why the functions do not necessarily determine topological structures is that many topological structures can fulfil the same function. For example, both negative autoregulation and type 1 incoherent feedforward loop serve the same function – speeding response time (Shoval and Alon 2010).

A unique virtue of design principle in systems biology is its generality, which satisfies the third condition – the certain invariant generalizations, rules, principles and formal constraints F limit and afford the possible designs. Compared to mechanism which targets the particular phenomenon, similar design principles are applicable to a large and broad class of biological phenomena, although there is variability at the level of mechanisms and at the level of networks structure. Before the advent of philosophical definition of mechanism, the deductive - nomological modeling of explanation is regarded as paradigmatic scientific explanation in the earliest times. According to this kind of explanation, the explanans include premises information concerning the initial conditions and the general laws, through a valid deduction, the conclusion is the explanandum to account for the phenomena. This kind of explanation could unify different physical phenomena by appealing to the same law of nature. After this explanation’s failure to satisfactorily account for explanatory relevance, a variety of new scientific explanations emerged due to the heterogeneity nature of different scientific theories and practices. Among these explanations, the mechanistic explanations interpret the scientific endeavours in life science as enterprises searching for diverse mechanisms that explain targeted phenomena.

From the observations on the main features of biological disciplines, we find that the mechanisms underlying biological systems are diverse. The reason behind are that biological organisms undergo through a course of evolution in which the evolutionary contingency and organismal variations play major roles. On the one hand, mechanistic explanations are very heterogeneous and universal rules of biology hardly exist. On the other hand, general principles are not hard to find in biology, like higher order laws, optimality principles, organizing principles (Green 2015). Systems biology takes a rather different position. Finding general organizational principles in systems biology has its own theoretical and practical significance. In systems biology, an unusual theoretical effort in systems biology is to attempt to uncover one kind of general principles – design principles as general principles of biological organization across many specific organisms.

6. My reply to possible criticism

Green and Jones made a comment on Ma’s finding that both the negative feedback loop and the incoherent feedforward loop are possible structures that can achieve then same function – robust perfect adaptation. Although they agree that both design principle of integral feedback control and design principle of incoherent feedback loop can achieve the same function, they said that ‘… a recent review argues that both are instances of integral control that exemplifier how the internal model principle is satisfied in all known biological case’ (Green and Jones 2016). It means that integral control is still necessary for achieving robust perfect adaptation, which could not only be realized through the topological structure of negative feedback loop but also the incoherent feedforward loop. Moreover, the incoherent feedback loop is mathematical identical to the integral feedback loop through a global transformation of coordinates, under certain technical assumptions (reference). Thus, these two design principles can be merged into a broader category of integral control, which is a special instantiation of internal model principle. Under this line of reasoning, Green and Jones intended to rescue design explanation within systems biology in face of other possible design principles for performing robust perfect adaptation.

I will look at their argument by in the definitive framework of design explanation and see whether this line of reasoning works. I will still use the case of bacterial chemotaxis as the basis of the discussion. Condition (1) is to classify organisms which share the same design and functional property as a group. In our case, the type of organisms N share the design of negative feedback loop and the function of robust perfect adaptation, which all of us will agree on this point. Green and Jones’ line of reasoning is different from Braillard’s argument in condition (2). While Braillard takes the invariant generalization that integral feedback control is not only sufficient but also necessary as the formal constrain in condition (2), this time Green and Jones take the engineering principle of integral control as the formal constraint. In terms of topological structure, the engineering principle of integral control corresponds to two topological structures – negative feedback loop and incoherent feedforward loop, whereas the design principle of integral feedback control only corresponds to one topological structure – negative feedback loop.

The functional dependency between negative feedback loop and robust perfect adaptation still can’t be inferred in condition (3) by Green and Jones’ understanding of condition (2). Although incoherent feedforward loop can be transformed to negative feedback loops through mathematical reconstruction, however, this mathematical transformation bears no biological meaning (Shoval, Alon, and Sontag 2011). The transformed negative feedback loop is a special kind of negative feedback loop – it has only eigenvalues, thus it can’t perform the property of general integral feedback loops – damped oscillatory behaviour. More importantly, incoherent feedforward loops lose its topological property in this pure mathematical transformation.

Negative feedback loops and incoherent feedforward loops are different designs or topologies in terms of graph theory, Negative feedback loop motif can be represented as a directed graph, consisting of three vertexes a, b, c and three edges. An edge between the vertexes a and b is represented by the ordered vertexes pair (a, b). Edges are often signed. The edge X"Y means X activates Y, Y:X means X represses Y. Negative feedback loops can be presented as graph G’ with vertex set N’ = {a, b, c}, edge set E’= {(a, b), (b, c), (a, c)} and corresponding edge types (", ", :).

However, this is where design explanation cares about, because design explanation aim to explain why does this particular circuit appear rather than any other conceivable designs. This functional dependence still can’t answer general design questions like why this design – negative feedback loop appears rather than other designs – incoherent feedback loop or state-dependent inactivation or antithetical feedback control.

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1. Design here involves no designer which may suggest creationism, and it means the arrangement of structural details. [↑](#footnote-ref-1)
2. Graph theory attempts to model objects and their relations in terms of graphs, which consist of nodes and lines connecting these nodes. [↑](#footnote-ref-2)
3. Evolutionary contingency refers to that chance is an important factor in the evolutionary course, like neutral evolution or genetic drift. [↑](#footnote-ref-3)
4. Evolutionary convergence means that the engineering solution to particular problems are similar. [↑](#footnote-ref-4)
5. I correct F in the original paragraph into P because the formal dependency relation is supposed to between T and P. After this revision, this design explanation can be subsumed under a broader category of constraint-based explanation as Green and Jones intend to, otherwise it won't do. [↑](#footnote-ref-5)
6. Integral feedback control, along with proportional and derivative control, consist the established principles of feedback control in engineering. [↑](#footnote-ref-6)
7. In integral feedback control, a controller integrates the error between the output and the desired output over time to produce the desired output. [↑](#footnote-ref-7)
8. Control system is a dynamical system in engineered machines, which uses control theory as a solution to specific control requirement. [↑](#footnote-ref-8)
9. Barkai and Leibler’s model is built on a series of general assumptions on the mechanistic details. The first assumption is that CheB only demethylates active receptors rather than inactive receptors. If CheB also demethylates inactive receptors with the same associate rate of active receptors, and rest conditions remain the same, the adaptation can’t achieve precision not to mention robustness. The second assumption is that the kinetic rate constants of CheR and CheB have nothing to do with the methylation state and whether the receptors are combined with attractants or repellents. The third assumption is that methylated receptors can’t be affected by the activity of unmethylated receptors. The last assumption is that concentration of bound CheR is independent of the level of how the receptors are combined with attractants or repellents. Given other conditions remain the same, failure to relax any of the above assumptions will not produce desired robust perfect adaptation. [↑](#footnote-ref-9)
10. J = - D A C/x, J is the rate of diffusion (mole/s); D the diffusion coefficient (cm2/s); A the surface area available for diffusion (cm2); x the distance of diffusion (cm); C the concentration difference over that distance (mole/cm3). [↑](#footnote-ref-10)