Forthcoming in: *Modeling the Possible. Perspectives from Philosophy of Science*, edited by Tarja Knuuttila, Till Grüne-Yanoff, Rami Koskinen, and Ilwa Sjölin Wirling. Routledge (expected 2025)

Penultimate draft

Chapter 6: Modeling the Biologically Possible: Evolvability as a Modal Concept

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Abstract

Biological modalities, i.e., biologically possible, impossible, or necessary states of affairs have not received much attention from philosophers. Yet, it is widely agreed that there are biological constraints on physically possible states of affairs, such that not everything that is physically possible is also biologically possible, even if everything that is biologically possible is also physically possible. Furthermore, biologists use concepts that appear to be modal in nature, such as the concept of *evolvability* in evolutionary developmental biology, or "evo-devo." The present chapter investigates what kind of modality underlies the concept of evolvability. This concept tries to capture the capacity of an organism or a lineage to sustain genetic changes that enable it to evolve or to evolve adaptively. The basic idea of the proposed approach is to construe evolvability as a kind of accessibility in a modal space. The difficult part is to specify this modal space and the relevant accessibility relation. While there may not be a general way of defining such a relation, there exist model systems for which it is possible, e.g., evolving small RNAs. The modal space in such cases turns out to be quite distinct from those constructed

by philosophers, e.g., David Lewis's similarity metric for possible worlds. Even though the biological case examined here is quite special, attending to the way in which biological possibilities are modeled in this case harbors some general lessons about biological modalities, in particular their dependence on the explanatory goals of the models modeling modality.

1. Introduction

An elephant with feathers doesn't seem to be as equally impossible as a flying elephant. Laws of physics prohibit the latter but not the former. Yet an elephant with feathers would also be a strange creature because it is a mammal, not a bird or a dinosaur, and only the latter have evolved feathers. In fact, feathers are more recent in evolutionary history than the last common ancestor of mammals and birds. They are thought to be homologous to hair and scales. Mammals have evolved hair from the common primordial structures that gave rise to feathers in the dinosaur lineage leading up to contemporary avians, this is why the feathered elephant is biologically impossible. It would require both a reversal and a highly similar rerun of evolutionary turns that happened long ago, which is unlikely in the extreme (Beatty 1995; 2016). Hence our confidence that a feathered elephant is biologically impossible, at least relative to our actual evolutionary history.

While judgments of biological possibility are common in and outside of biology, the nature of these modalities has not been much studied by philosophers. A notable exception is Dennett (1995), who construed biological possibility as accessibility in a complete space of possible genomes that make up what he calls the "Library of Mendel." Max Hindermann (né Huber) has developed Dennett's idea into a full-blown modal logic (Huber 2017). Others have criticized the whole idea of trying to define a complete space of *all* biological possibilities (Maclaurin and Sterelny 2008), even if it is only relative to a given organism. However, this does not rule out possibility spaces that define a relevant set of possibilities given some

explanatory goals, such as morphospaces in evolutionary biology. Morphospaces are representations of a range of possible forms that some biological structure, for example, a coiled snail shell, can take. The extent to which regions of such a space represent existing forms can give evolutionary biologists indications as to where to search for evolutionary mechanisms such as natural selection or developmental constraints, as shown by Maclaurin and Sterelny (2008) and Huber (2017).

While the modeling of modalities is increasingly being studied by philosophers of science (e.g., Ladyman 1998; Ijäs and Koskinen 2021; Knuuttila 2021; Sjölin Wirling and Grüne-Yanoff 2021a, 2021b), there have hardly been any attempts to clarify the modalities underlying biological concepts such as evolvability. The rest of this chapter will present such an attempt. In the following section, I will give some basics about evolvability and a biological field where it plays a central role, namely evolutionary developmental biology or "evo-devo." In Section 3, I will give a more detailed account of a model system in which evolvability can be assessed. Section 4 will then present my account of evolvability as accessibility in genotype-phenotype map space. In Section 5, I will analyze what kind of possibility might underlie biological models of evolvability. In the concluding section, I will draw out some general lessons from my analysis of this somewhat special case from evo-devo.

2. Evolvability Explanations

Evo-devo addresses questions such as: How can the same genetic mechanisms give rise to different organismal forms? How did specific developmental programs evolve? How do developmental processes affect evolutionary trajectories (Love 2020; 2024)? The concept of evolvability has been introduced to capture what is thought to be an intrinsic feature of a type of organism, namely its capacity to evolve (Alberch 1991; Kirschner and Gerhart 1998; Love 2003; Brigandt 2015; Villegas et al. 2023). This capacity is closely linked to the ability to

produce heritable phenotypic variation such that it can sustain genetic modifications that remain stable over several generations (Kirschner and Gerhart 1998). Evolutionary forces such as natural selection or drift can only act on the gene variants that arise in a population, but many gene combinations may never occur because they don't allow the organism to develop to adulthood, i.e., to the reproductive stage. Thus, evo-devo must attend to developmental mechanisms and seek to understand how genetic changes can modify these mechanisms such as to produce different viable phenotypes, which may then undergo natural selection or genetic drift. These mechanisms may show a bias for some forms or some regions of a morphospace, thus explaining certain evolutionary patterns non-adaptively (Gould and Lewontin 1979; Brakefield 2006). Of course, such biases can also combine with natural selection and/or drift to explain certain evolutionary patterns (Novick 2023). Such biases are also called "constraints" and come in different forms, including constraints on form and constraints on adaptation (Amundson 1994).

It is important to realize that there is not just one but several concepts of evolvability in biology. Love (2003) distinguishes between evolvability$_U$ and evolvability$_R$. The former, which is used mainly in quantitative evolutionary genetics, means the ability to respond to natural selection, which depends on heritability and additive genetic variance. It is considered to be a population property. The second term designates that which explains the differential evolutionary success of lineages, usually considered to be an intrinsic disposition of a type of organism. The literature contains many differing notions of evolvability (Hansen and Pélabon 2021), but they may be seen as all falling under one or the other side of Love's twofold distinction.

Philosophers attending to the concept of evolvability have invariably classified it as a *disposition*, analogous to fitness in the theory of natural selection (Brigandt et al. 2023). For example, Brown (2014) identifies evolvability with the probability $E = Pr_{x,b}(F_t)$ that a set of features F arise at future time t given the population x and its environment b at some starting

point. Evolvability thus construed is a dispositional property, more precisely a *propensity* that results from the joint causal influences of factors internal to the organisms making up population *x*, given some environment *b*. The environment should be viewed as belonging to the manifestation conditions of the disposition, thus making evolvability an intrinsic property of a population (as most biologists insist).

A full appraisal of this account is beyond the scope of this chapter; my aim is rather to provide an alternative view. Nonetheless, I will point out some possible lacunae in the propensity view.

My approach in this chapter is to take seriously the idea that evolvability is essentially a *modal* concept that is used to make claims about what is evolutionarily possible. When we attend to the way in which the concept is used in biological practice, as we should (Brigandt 2015), we can see that it is often tied to a typical explanatory strategy, which I shall refer to as an *evolvability explanation*. This strategy takes as a starting point the assumption that evolutionary change, or at least some kinds of change, is *prima facie im*possible or has a low degree of biological possibility (if it comes in degrees). Then, an evolvability explanation postulates a mechanism that explains how a certain kind of change is possible after all. This explanatory structure is also known as "how-possibly explanation" (Dray 1957), however, diverging accounts of such explanations have been given (Reiner 1993; Verreault-Julien 2019; Grüne-Yanoff 2013). What matters here is that how-possibly explanations clearly involve modalities (Sjölin Wirling and Grüne-Yanoff 2021a).

Such a construal of evolvability explanations nicely fits the view that evolvability explanations provide a solution to an *evolvability problem*. This strategy is explained very clearly in Pavlicev and G.P. Wagner (2012a). They begin by noting that organisms can only adapt to new environments if there are individuals who are "suited to survive under the new circumstances" (231). They then define as "evolvability" as the "ability of a population to cope with the changing environment by adaptation." But adaptation by natural selection is only

possible if random mutation delivers the "suited individuals." Now, random mutation can have "an incredible number of effects on the phenotype, and most of them will be deleterious under any circumstances, if not lethal" (ibid.). Thus, the following problems arise:

> How does such random genetic change produce the "right" kind of deviation often enough? How is change possible where multiple mutations are necessary but intermediate steps have no apparent advantage? How probable is adaptation if only some of the traits should be changed, without affecting those that are already in place? (Pavlicev and G.P. Wagner 2012a, 232).

Thus, *prima facie* it seems exceedingly unlikely that random mutation should be able to generate complex adaptations. This is a problem that Darwin had already been grappling with. The problem is that chances are there will likely be no "suitable individuals" alive, and if there are, they are not likely to have an advantage, so there is nothing that natural selection can do.

Now enter what I call evolvability explanations. Such explanations describe a mechanism or a set of mechanisms that can produce the necessary genetic variants for natural selection to act upon. Such mechanisms are frequently represented by using a so-called *genotype-phenotype* or *GP-map*, an important theoretical idea in evo-devo (Alberch 1991). This map specifies for a type of organism what phenotypes (usually from a range of forms that are chosen in view of a specific research problem) can be produced from what genotypes. The GP-map is determined by developmental and physiological facts about the given species. More precisely, the map is a highly abstract summary of these facts. Pavlicev and G.P. Wagner (2012a, 232) describe it as a "statistical summary" that abstracts away from the myriad of developmental and physiological processes that occur in a living organism. Framed in this way, the question becomes what kinds of GP-map structures give rise to high evolvability. Furthermore, there is the question of whether evolvability can itself evolve or evolve under

selection, which I will leave out for now for the sake of simplicity, even though it is also a part of some evolvability explanations.

One proposed mechanism for high evolvability is that of a *modular* GP-map, an idea originally due to Rupert Riedl (G.P. Wagner and Altenberg 1996). This means that the map is organized in such a way that pleiotropic effects mostly affect traits that form a complex or module with a distinct selected function (e.g., locomotion, visual perception, etc.) and fewer traits from a complex serving a different function. In other words, pleiotropy is not randomly distributed across all the traits of an organism.[1] This allows selection to act on the trait without affecting other traits and thus incurring fitness costs by pleiotropic effects. Modularity thus answers the third question raised by Pavlicev and G.P. Wagner (2012a), to wit, how adaptation can change only some traits and leave those already in place intact.[2] Modularity removes a major theoretical obstacle to the possibility of adaptation and thus provides what a call an evolvability explanation, which is a solution to an evolvability problem. The extent to which it is responsible for adaptive change relative to other proposed mechanisms that can compensate for deleterious pleiotropic effects is subject to debate (Hansen 2003; Pavlicev and G.P. Wagner 2012b).

Another classical idea is that of *robustness* (also called *canalization* in some older literature). When used in an ontic sense, robustness signifies a kind of invariance against perturbations. In biology, two important kinds of robustness are (1) invariance of the phenotype against environmental perturbations and (2) invariance of the phenotype against genetic mutation (A. Wagner 2012; 2013). I shall focus here on the second kind of robustness. It

[1] I owe this formulation to James DiFrisco.

[2] See Herbert Simon's (1962) parable of the two watchmakers one of whom is more efficient because he builds his watches in a modular fashion, allowing him to conserve modules already assembled. I am indebted to James DiFrisco for suggesting this analogy.

features centrally on an important kind of evolvability explanation. Biological systems at all levels of organizations are capable of genetic variation that does not manifest itself at the phenotypic level. There are several mechanisms behind this phenomenon. First, there are so-called "silent" point mutations in the coding region of genes. These do not alter the protein molecule encoded either because they are located in a non-coding region such as an intron (which is spliced out after transcription), or because they occur in the third position of a codon or base triplet, which, due to the redundancy of the genetic code, makes no difference with respect to the amino acid moiety encoded. Second, there are gene mutations that do change one or a few amino acids in the protein encoded, but without affecting the protein's shape, function, and stability. Third, some mutations are recessive, i.e., they have no phenotypic effect when there is a second copy of the same gene present (in diploid organisms). Fourth, there are point mutations that neutralize each other when they occur in *trans* (i.e., in a distinct copy of the same gene present on a different chromosomal unit), a phenomenon known as "intra-allelic complementation." Fifth, there are molecules (protein or RNA) that are functionally redundant because there is another molecule that can take its function when their gene harbors a mutation affecting its function.

These five sources of robustness have been known for a long time, and they can increase evolvability by allowing genetic changes to accumulate without affecting the host. However, their effect on evolvability is a kind of side effect of the basic genetic mechanisms.

In addition, there are more specific molecular mechanisms that can increase robustness. A classic study in *Drosophila* genetics (Rutherford and Lindquist 1998) demonstrated a role for the heat-shock protein Hsp90 in increasing evolvability in fruit flies. Hsp90 is a so-called "molecular chaperone," which means that it helps proteins to fold into their most stable shape. A loss-of-function mutation in its gene leads to many misfolded or unfolded proteins (which tend to be sticky, hence the name "chaperone" – it prevents inappropriate protein-protein interactions). When the gene is mutated in fruit flies, laboratory populations show a significant

increase in phenotypic variation, which is not due to genetic variation. Rather, it seems that functional Hsp90 masks a lot of genetic variation that is already present in the population by stabilizing mutant proteins. Thus, Hsp90 is part of a mechanism that directly increases robustness and hence evolvability. It allows mutant organisms to survive and even reproduce that harbor genetic mutations that may someday become valuable and hence selected for.

Robustness comes in different forms and many mechanisms can increase robustness. In addition to the molecular mechanisms mentioned, there are also mechanisms at the level of gene regulatory circuit dynamics that are able to buffer mutations in non-coding regions (cis-regulatory elements) affecting transcription rates. Feedback circuits helping the developmental system to buffer perturbations abound in multicellular organisms (Siegal and Leu 2014). However, it seems that the principle is always the same: Robustness solves the first and second evolvability problems according to Pavlicev and G.P. Wagner, namely the problem of ensuring that useful mutations occur often enough in a population (and are also carried along into future generations even if they are potentially harmful or neutral), and that changes that require multiple mutational steps can occur.

I will discuss a specific robustness mechanism, namely so-called neutral networks, in the following section in more detail. For now, let us note that modularity and robustness are very general and abstract types of organizing principles that make adaptation (as well as evolutionary novelty) possible. They provide solutions to an evolvability problem and thus "possibilify" a process that seems *prima facie* impossible. I believe that this is a widespread type of explanatory reasoning also in biology,[3] and that at least some explanations involving evolvability can also be understood in this manner.

[3] Here is an example from community ecology: We have *a priori* reasons to think that only species with the same food and habitat requirements can survive in the same place because

I would also like to point out the abstract nature of such concepts as modularity and robustness. These concepts apply to a wide range of biological mechanisms (such as the Hsp90 mechanism and the neutral network mechanism to be discussed in the next section) and show what a series of quite distinct mechanisms have in common. In the present context, they make certain types of processes possible that seem impossible without them, given some theoretical assumptions. In the following section, I will take a closer look at an evolvability explanation of the robustness type.

3. Small RNAs as a Model of Evolvability

While in most cases vast regions of the GP-map – even its dimensionality – remain unknown, there exist simple model systems where a GP-map can be constructed. An example of such a system is small RNAs, i.e., ribonucleic acids with a length of usually <100 base pairs. Not life forms of their own, small RNAs play various roles within all types of living cells. For example, some of them work as transfer-RNAs in protein synthesis. They can form rather complex secondary structures due to Watson-Crick-type base pairing interactions within the same molecule. The secondary structure basically consists of a set of intramolecular base

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ecological models demonstrate that there must always be one species that outcompetes all the others in a winner-takes-it-all type of competition. But empirical evidence clearly shows that very similar species can and do peacefully co-exist in one and the same habitat. This paradox was resolved by postulating and verifying various coexistence mechanisms that prevent interspecific competition from running its course (Weber 1999). The case is similar to the classic how-possibly explanations in that we have some kind of a theorem according to which some phenomenon is impossible, and then mechanisms are suggested for how it can be possible after all.

pairings (due to hydrogen bonds) and determines the RNA's three-dimensional shape as well as its biological function. Typically, such RNAs form various hairpin- and loop-like structures (see Figure 1). In some cases, a huge number of different RNA sequences can give rise to the same three-dimensional shape, which may differ in free energy (i.e., thermodynamic stability).

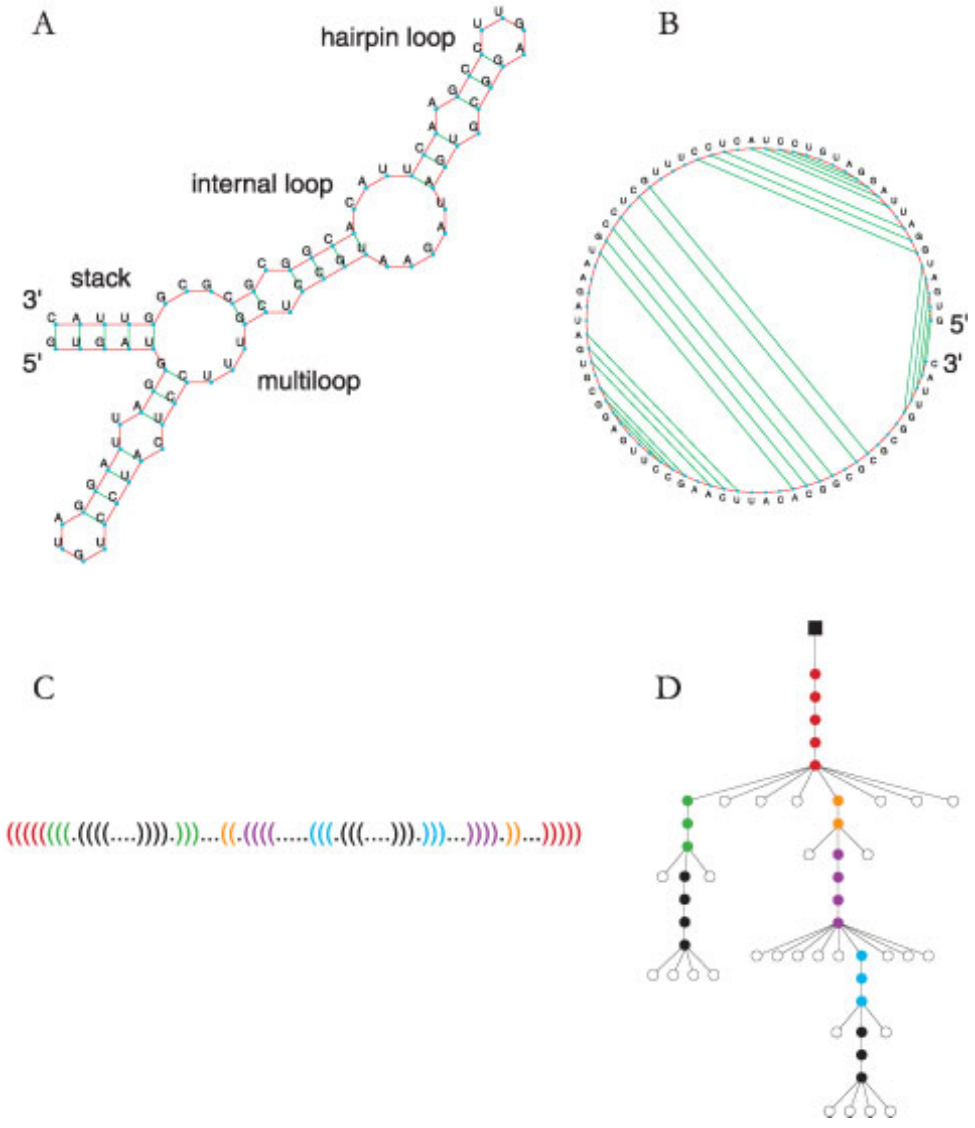

Figure 1. Secondary structure in small RNA molecules is defined by intramolecular base pairings that generate various loop-like structures. The molecule's three-dimensional shape is determined by the secondary structure. Many different sequences can have the same shape, and

even slight variations in secondary structure do not necessarily alter the shape. Image reproduced with permission from Fontana (2002).

Small RNAs are models for evolvability for the following reasons: (1) There is a *genotype-phenotype distinction*. The genotype is the nucleotide sequence of the RNA (or the DNA sequence of the gene that encodes it), while the phenotype is the secondary structure and the three-dimensional shape. The folding up of the molecules from a chain of ribonucleotides to a three-dimensional structure is analogous to the process of development. The relation of genotypes to phenotypes is many-one.[4] (2) RNAs are capable of evolving, i.e., of being replicated and stable over generations with modifications. (3) There is a reliable mapping of genotypes into phenotypes, given suitable conditions (temperature, ionic strength). (4) This mapping is epistemically accessible for a large number of different sequences, thanks to powerful biocomputational tools, enabling researchers to predict secondary structures as well as three-dimensional shapes from pure RNA sequence information.

It is especially the fourth feature that distinguishes the small RNA model from whole organisms and that makes it suitable for studying evolvability. The epistemic accessibility of a vast number of genotype-phenotype relations allows for a kind of modal modeling, namely computing the GP-map for a large number of possible sequences most of which will never be realized. For illustration of the sheer magnitude, if one were to make just one single molecule of every RNA sequence with a length of 79bp the aggregate of them would weigh more than the Earth (Manrubia et al. 2021)! Of course, only a small subset of this vast space of possibilities can be modeled. Fontana and Schuster (1998) built a computational model for studying so-

[4] In more complex cases, its rather many-many, but here the genotype pretty much determines the phenotype, at least under normal conditions (temperature, ionic strength).

called *neutral networks* in the space of possible genotypes. These are regions in genotype space that map into the same phenotype, as defined by a three-dimensional shape (see Figure 2).

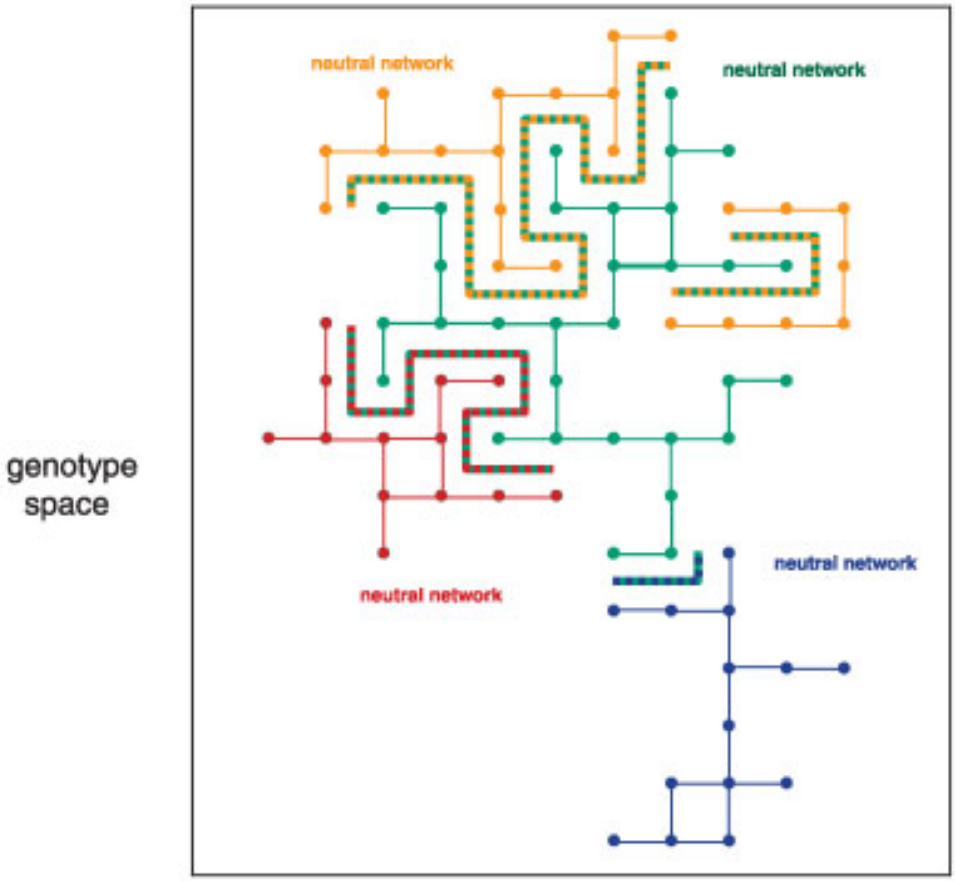

Figure 2. This map represents a simple genotype space for small RNAs. Each point in this space represents a possible RNA sequence. Neighboring points can be reached via a single one-nucleotide mutation. Each colored network in this space represents a series of changes that do not affect the molecule's shape and are therefore selectively neutral. Different colors represent different shapes, so a transition to a network shown in a different color here is not necessarily selectively neutral. This map shows that some transitions are likely because a random step out of a neutral network will take into a specific neighboring network (but not necessarily vice versa). Some changes are extremely unlikely because they would require several mutations to occur to transition from one network to another (see Figure 3). Image reproduced with permission from Fontana (2002).

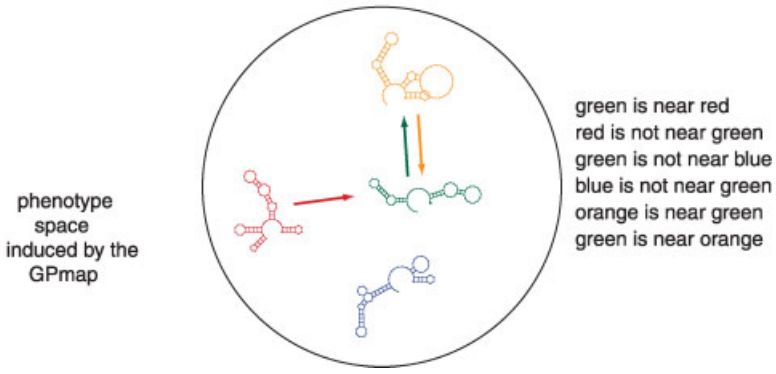

Figure 3. A GP-map for the neutral network shown in Figure 2, showing the possible transitions between different phenotypes (i.e., different shapes of the RNA molecule). Image reproduced with permission from Fontana (2002).

The neutral network model provides a solution to the problem of how a molecule can evolve into a new shape (and potentially acquire a new function) by a process that requires several mutational steps. Throughout the process, that is, until the final mutational step, the molecule retains its old shape and therefore its old function (should it have one), thus providing an explanation for the evolvability of these molecules. Of course, the same result could be reached by following a different path in the sequence space, but paths that lie outside the neutral corridors might disrupt the molecule's function (and therefore stop the process short, because the organism with disrupted small RNAs might not be viable). Thus, the small RNA model provides a simple and tractable model of evolvability. In the following section, I will examine the relationship between evolvability and biological possibility within the scope of this model.

4. Evolvability as Accessibility in Genotype-Phenotype Map Space

The neutral corridors in the GP-map space show which genotypes are accessible from any original genotype by a series of random genetic changes that are (1) not too unlikely to occur jointly in an actual population and (2) compatible with development and reproduction. Namely, those genotypes that are located in an adjacent region, with respect to the original genotype, of the GT-map are accessible. I would like to suggest that this kind of accessibility can be used to define the relevant sense of possibility that underlies evolvability explanations in evo-devo. In order to see this, let us compare it to an account of accessibility that has been used to clarify the concept of biological possibility by way of a modal logic.

Probably the most elaborate attempt of this kind so far has been provided by Max Hindermann (né Huber) in his Ph.D. thesis (Huber 2017). Hindermann's modal logic refines and formalizes an idea presented by Dennett (1995). In order to conceptualize biological possibility, Dennett invented the "Library of Mendel" (LoM), a library that contains all the genomes that can be constructed from the four DNA bases A, T, C, and G (inspired by Jorge Luis Borges's "Library of Babel"). A "reader-constructor" maps genomes from the Library of Mendel to phenotypes. Biological possibility is then defined by Dennett in terms of an accessibility relation for genomes:

> X is biologically possible if X is an instantiation of an accessible genome or a feature of its phenotypic products.

It is clear in Dennett's account that biological possibility is always relative to a given genome, *g*. A biological organism is possible at *g* to the extent in which it is the phenotypic product of a genome *g'* that is accessible from *g* (e.g., by a series of point mutations or sequence rearrangements). The more accessible *g'* is from *g*, the more possible its phenotypic product at *g*.

Dennett did not specify the relevant accessibility relation. This is where Huber's (2017) account comes in. He first reformulates the Library of Mendel as a relational structure (61):

> The Library of Mendel is a relational structure $\langle \Sigma_M, R_M \rangle$ where the domain is the language of the Library of Mendel *M* and the binary relation is the accessibility relation R_M.

The language of the Library of Mendel consists of an alphabet containing the four nucleotide bases A, G, C, and T. Biological possibility is then defined in terms of satisfaction of the binary relation (61):

> Some *x* is biologically possible at $g \in \Sigma_M$ if and only if there is some $g' \in \Sigma_M$ such that gR_Mg' and *x* is an instance of *g'* or a feature of the phenotypic products of *g'*

Finally, Huber provides an interpretation of the accessibility relation R_M:

> For $g, g' \in \Sigma_M$, gR_Mg' if and only if there is a solution to a string editing problem with respect to *g, g'*

A string editing problem is the problem of obtaining some string of symbols from another string by the least costly set of edit operations. For example, the string 'AACTTC' can be obtained from the string 'GGCTTC' by an edit operation that replaces all Gs in the string with As. The same sequence could also be obtained by first replacing all Cs with As, then changing back all As to Cs, and finally replacing all Gs with As. The latter edit operation would be more costly. For most cases, we can identify the number of edit steps needed with the cost, in other words, the cost of each step is identical. However, there might be cases where the cost varies with the kind of change introduced. For example, we could consider operations that cannot be brought about by an existing biological mechanism as being more costly.

Alternatively, we could make the edit cost depend on the amount of metabolic energy needed. In any case, the solution to a string edit problem depends on the assumption of a cost function, and the space of biological possibility is going to be relative to such an assumption.

This formulation in terms of string editing allows Huber to use the string edit distance as a measure of possibility. Several such measures exist; for example, the *Levensthein distance* is defined as the minimal number of operations needed to transform one string into another. As new genomes arise by mutation and recombination of existing genomes, the number of such changes needed to obtain a new genome from an existing one seems like a biologically relevant measure of accessibility.

Thus, in brief, according to Huber the fewer mutational or recombinational steps are required to create a genome g' from an existing g, the more accessible and hence the more possible the latter is with respect to the former. This seems well in line with the intuition that, whatever biological possibility is, it must be relative to a given organism or lineage and it must come in degrees.

I think that Huber's account may capture some relevant sense of "biological possibility;" however, I will argue now that it is not the sense that underlies the concept of evolvability. There are several differences. First, the most obvious one is that Hindermann's accessibility relation—let's call it "H-accessibility" where "H" stands for Hindermann—refers only to nucleotide sequence while E-accessibility ("E" for "evolvability") refers to sequences plus phenotype. This already implies that different modal concepts must be in play here.[5] However, it should be noted that something like the string edit distance is also a component of E-accessibility. In the models at hand, biologists used not the Levensthein- but the *Hamming distance*, which is the number of individual positions in which two strings differ. In the small RNA model, they define a "neutral neighbor" as a sequence that gives rise to molecular shape

[5] Thanks to Fabrice Correia for pointing this out to me.

α any sequence that gives rise to the same shape that can be produced by a single point mutation, i.e., has a Hamming distance of 1. This neutral neighbor will itself have neutral neighbors, and so on, until we arrive at a sequence that gives rise to a different shape β. The distance between α and β in phenotype space can then be defined as the transition probability that a sequence that folds into β is produced from an α-folding sequence by a series of random point mutations, which is proportional to the number of genotypes that fold into shape α that are adjacent to genotypes that fold into β (Stadler et al. 2001, 258). Thus, distance in sequence space—here measured by the Hamming measure—is necessary but not sufficient because even two close locations in sequence space could be in non-adjacent regions of the GP-map (see Figure 3 for an example).

A second difference is that the Levensthein distance is necessarily *symmetrical* because any string edits that can be used to obtain a sequence G' from sequence G can be carried out backward to produce sequence G from G'. By contrast, E-accessibility is not always symmetrical. In other words, there are evolutionary changes that are irreversible or that would take much more time than the corresponding change in the opposite direction (see again Figure 3 for an example). While this feature might seem counterintuitive, there are everyday examples that share this feature. Consider a map of Switzerland with Geneva sitting at the tip of the appendix in the extreme West of the country. The canton of Geneva is surrounded by France (it shares about 150km of border with France and 4km with the only neighboring Swiss canton of Vaud). Thus, when you step outside Geneva at a random location you are very likely to find yourself in France. By contrast, when you step outside of France at a location randomly chosen

on France's entire national border you are, of course, not at all likely to be in Geneva. It's the same in the neutral networks. This kind of accessibility, too, is asymmetrical.[6]

Third, the Levensthein distance can be used to define a *metric space* with the string edit distance as the relevant distance function. By contrast, E-accessibility is non-metric, which is already implied by the fact that it allows asymmetric relations. However, even though E-accessibility is not technically a distance measure, a binary relation of nearness can nonetheless be defined, for example, by considering some shape α and all the shapes that are accessible from it by random events above a certain likelihood threshold as a neighborhood (Fontana and Schuster 1998).

The choice of this threshold is not arbitrary but is informed by biological considerations, namely mutation rate, population size, or time frame (Stadler et al. 2001, 258). This has to do with the epistemic purposes of these models. Their goal is to explain real evolutionary patterns. Therefore, they judge the possibility of certain changes under the actual conditions under which the evolutionary processes in question actually occur, which include the parameters just mentioned. Given enough time, a practically unlimited population size, and/or a sufficiently high mutation rate, any RNA shape could evolve from any other. But under real world conditions, including limited time and population size, some transitions will be so unlikely as to have no evolutionary significance. It is these transitions that are judged to be inaccessible

[6] The counterintuitive properties of the modal space may be attributable to its extremely high dimensionality. James DiFrisco also suggested to me an intuitive reason, namely that it is in general easier to break or obliterate a trait than to build one. R.A. Fisher (1930) has illustrated this idea with the example of a microscope: The more adjustable knobs it has for focusing the image, the less likely it is that turning them randomly will produce a sharp image. He also proposed a geometrical argument involving fitness landscapes why mutations with small effects are more likely to be advantageous than mutations with large effects.

and hence impossible by biologists. Thus, judgments of possibility and impossibility depend on the explanatory purposes of these biological models.[7]

The last feature also points us to the limits of a purely probabilistic construal of evolvability such as Brown's (2014) propensity account. While probabilistic considerations do play a role in evolvability explanations, as we have seen, the propensity account does not fully account for biological practice, because evolvability is often construed as a threshold property. Evo-devo researchers are interested in finding out "which evolutionary changes are possible or easy to achieve" (Hansen and Pélabon 2021). Probability considerations are often used alongside studying possibilities, so the two accounts are not mutually exclusive. But why would biologists talk about possibility if they were merely interested in how *likely* some changes are?

In the following section, I take a closer look at the relevant sense of modality.

5. What Kind of Modality?

In the previous sections, we have seen that evolvability and the underlying sense of possibility can be construed at least in some cases in terms of a kind of nearness in GP-map space. In this section, I will investigate further the nature of this space and compare the resulting sense of possibility with other conceptions of modality.

As we have seen, existing proposals concerning biological possibilities construe them as obeying a distance metric that defines a metric space or topology in the mathematical sense. This means that distances satisfy certain axioms including symmetry and the triangle inequality: distance(x,z) ≤ distance(x,y) + distance(y,z). The Hamming and Levensthein distances mentioned above define metric spaces; the Hamming distance if only point mutations are

[7] This does not imply that modal statements do not also depend on what is considered to be objectively the case, as Tarja Knuuttila has pointed out to me. There are possibilities that, while perhaps being objective, have no biological relevance (Weber, forthcoming).

considered and the Levensthein distance also for other mutational operations. No such metric distance is defined in the GP-maps of our example. It contains only a much weaker ordering relation, namely to a so-called *pretopology* which is defined by a system of neighborhoods and allows asymmetries.[8]

The modalities generated by the RNA models are also different from the standard philosophical account of modality due to Lewis (1979). This account tries to define the notion of nearness of possible worlds by considering how similar such worlds are to the actual world (@). Lewis proposed to measure this similarity in terms of how big a violation of natural laws or "miracles" would be required to transform a world into actuality. If it takes a bigger miracle to turn world *w* into @ than world *w**, then *w** is more similar or closer to @ than *w*. The magnitude of miracles is to be assessed by using a system of weights and priorities according to which avoiding (1) "big, widespread, diverse violations of law" take priority over (2) the maximization of the "spatiotemporal region throughout which perfect match of particular facts prevails", which in turn has more weight than (3) avoiding "even small, localized, simple violations of law", while (4) securing "approximate similarity of particular fact, even in matters that concern us greatly" are of "little or no importance" (Lewis 1979, 472). These priorities are intended to create a metric ordering relation for judging the truth of the value of counterfactuals such as "had I not taken the milk off the stove, it would have boiled." This counterfactual is true because, in the most similar possible world where I do not take the milk off the stove, which differs from actuality in a matter of particular fact as in (4), the milk would have boiled. This is true because this world is more similar to actuality than a world where, all of a sudden while I was answering the door, the boiling temperature of milk jumped to 300°C due to a localized violation of physical laws as in (3).

[8] A critical discussion of the various kinds of mathematical spaces used in evolutionary theorizing (sometimes metaphorically) can be found in Mitteroecker and Huttegger (2009).

What is notable is that this account of possibility does not take into account whether there is an actual *process* or *mechanism* that could transform a world into actuality.[9] This is evident in Lewis's appeal to miracles. What biologists are more often interested in, by contrast, are such alternative scenarios for the realization that there exist *naturally occurring biological processes* that *preserve the life of the organisms involved* (Weber 2017; forthcoming). In our RNA example, these two requirements are evident. The latter requirement is the reason why the biologists considered RNA genomes that fold into the same shape accessible because this means that the RNAs can preserve their function and thus sustain the life of their host organism. Furthermore, as we have seen, the biologists considered evolutionarily relevant such genetic modifications that are sufficiently likely to occur by a small number of spontaneous mutations in a realistic population size, mutation rate, and time frame. Any other possible scenarios are not relevant for the epistemic purposes of this inquiry and can therefore be disregarded. This includes in particular neighboring possible worlds according to Lewis's criteria as well as the possibilities characterized by the Levensthein-distance. In the concluding section, I will draw some general lessons from the present analysis of the small RNA models for evolvability.

6. Conclusions

I suggest that several lessons can be drawn from this inquiry into how evolutionary biologists model the possible. First, I have argued that the concept of evolvability that is used

[9] Alistair Wilson pointed out to me that there are more recent possible world semantics that are attuned to actual physics, e.g., Loewer (2012; 2020), however, I think my point that these accounts completely ignore biological processes stands.

in the type of evolutionary models considered here contains an underlying modality that is distinct from any other kind of modality that has previously been postulated by philosophers (but related to my notion of biological normality, see 2017, forthcoming). Modality or biological possibility in this sense is a kind of accessibility in GP-space, a relation which in some cases has unusual properties including asymmetry and the fact that it does, mathematically speaking, not form a topology but only a *pretopology*. This sets it apart from standard accounts of possibility, which posit metric modal spaces.

Second, the present analysis shows that judgments of possibility in biological models depend on the epistemic purposes of these models. Their purpose is to account for the phenomena, i.e., evolutionary patterns such as directionality and punctuated equilibria. For this purpose, biologists working on the RNA model examined here needed to find out how to divide up the vast space of nearly endless variations of RNA sequence not only in regions that are close in terms of Hamming- or Levensthein distance – which are still vast – but which are also safe to travel for real evolving populations and can be traversed in a reasonable amount of time under the given constraints (mutation rate, population size). Thus, the explanandum phenomena and the evolutionary conditions of real populations determine what possibilities from the endless frontier of the Library of Mendel are *relevant*. Possibilities that are not relevant in this way do not enter into the picture and are therefore not subject to biological modeling. This includes also the modalities created (or picked out, if you prefer) by an accessibility metric such as David Lewis', which was constructed in order to account for the truth values of counterfactual conditionals, for example, in order to give a reductive account of causality (Lewis 1987). Philosophers of causality have largely abandoned the latter project (Woodward 2003). The extent to which the modal structures examined here might be able to underwrite

justified counterfactual statements (not necessarily causal) about evolution[10] is an open question that is beyond the scope of this chapter.

Third, due to the special model system considered—small RNA molecules—it might be suggested that the biological possibilities examined here are not distinct from physical or "nomological" possibilities. After all, we are dealing with molecular species which behave in accordance with physical-chemical laws. I do not want to deny this, and I do not want to stay too attached to the terms "biological" and "physical", however, it should be noted that the possibilities examined here are relative to taking a certain perspective, which is typical for biology. I am talking about a *functional* perspective. In the models examined here, this perspective manifests itself in the focus on shape-preserving transitions, which serves as a stand-in for function preservation. As I have argued, the biologically possible is constrained by the need to preserve the life of some organisms under the changes considered. This usually means that biologists will consider large regions of the modal space irrelevant because nonviable organisms will not have any influence on future generations. To use an extreme case as an illustration: If getting from one viable form to another would require evolution to transition through some lethal form or a form with meager chances of survival, then this is not an evolutionarily possible path and hence not a biological possibility, even though the resulting end form may itself be viable and the two forms may even be very close in genotype space. These constraints on possibility result from taking an evolutionary perspective and may not arise if one takes a purely physical or chemical perspective.

The general conclusions drawn here are also applicable to more complex examples of evolvability from evo-devo. It must be admitted that the case of the small RNA models discussed here is quite special, not only because of the simplified nature and the availability of a complete GP-map, but also because neutral networks are not the only mechanism that makes

[10] The existence of such statements is controversial; see Beatty (1995).

for a highly evolvable system. As we have seen, neutral networks may be described as a realization of a broader phenomenon called robustness, which in this context means a kind of (phenotypic) invariance under perturbations. If a biological system is not able to buffer, to some extent, variations of its genome such as to allow for larger reconstructions it will never be able to give rise to novel forms (Pavlicev and G.P. Wagner 2012a; A. Wagner 2013).[11] Thus, only a tiny bit of the vast space of possible genotypes can be realized by evolution. While our discussion in this chapter has focused on a particular type of model system, namely small RNA molecules, research using other computationally tractable systems such as protein folding, artificial life, or transcription factor binding has reached similar conclusions (Manrubia et al. 2021). There are thus reasons for thinking that the modal spaces for a broad range of biological systems resemble those that I have examined.

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[11] James DiFrisco points out that robustness will also buffer against beneficial mutations, thus potentially preventing adaptive change. I am not aware of any general solutions to this problem. In the model discussed here, it is simply assumed that some possible leaps from one neutral corridor to another will be advantageous to the organism, although this is not represented in the model.

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