

Novelty in Evolution

**Green Paper for Bio-Evolutionary Advanced Concepts for NASA
(BEACON)**

WALTER FONTANA
SANTA FE INSTITUTE

walter@santafe.edu

30th September 2001

Contents

1	Novelty in Evolution	1
2	Some questions	4
3	From life to a technology of organization	5
4	Research examples	7
4.1	RNA folding and evolutionary dynamics: Evolution and development at the level of a single molecule	11
4.2	Abstract Chemistry: Organization as a self-maintaining network of transformations	14
4.3	Self-rewiring signaling networks: Organization as distributed control	16
5	References	18

1 Novelty in Evolution

What is novelty? Novelty is something that hasn't been there before. But this only shifts the problem, since it presupposes criteria for sameness on the basis of which something can be established to be non-trivially different from that which already exists. To distinguish novelty from more of the same isn't a simple affair. United States patent law defines novelty by a series of complex definitions (35 U.S.C. §102). In essence, an invention lacks novelty, if "prior-art" satisfying its description exists. In addition, a novelty is unpatentable, if it is "obvious". Needless to say, virtually every word in the definitions of novelty has been litigated, and a large body of caselaw exists to govern their interpretation and applicability.

No less are the difficulties in defining novelty for organismal evolution. When is something a true novelty rather than a variation on an existing theme? And what are the "somethings" that novelty can range over?

The "somethings" are features at different levels, most prominently the genetic (molecular), structural (morphological) and functional (metabolic, regulatory and behavioral) level. There is a long tradition, distilled into accepted methods, of establishing sameness (and thus novelty) by comparing gene sequences as well as morphological, anatomical and developmental features. These different methods more or less agree in their basic outcomes. Yet, underneath the surface, the issues surrounding sameness in biology are tricky. Sameness is not aligned across levels. The same structural feature can have different functions in different organisms¹ and different structures can have the same function².

Sameness across organisms exists in part because of common ancestry and in part because of independent convergent evolution. The remarkable fact, however, is the maintenance of sameness in spite of changing evolutionary pressures. The organizational characteristics of many feature remain invariant, despite the forces of selection acting to adapt them to different functions. It is this invariance that permits to establish the correspondence of two features that have diverged in evolution, such as the forelimbs of bats and birds. What underlies this invariance? What breaks it? How do new invariances

¹For example, the articular and quadrate bones in the mandible of reptiles are the malleus and incus of the mammalian ear.

²For example, different enzymes that catalyze the same reaction.

arise³?

In contrast to patent law, evolutionary biology faces the question of the origin of novelty. The issue here is not the optimization of extant structures, functions or organizations, but rather how these come into being in the first place. Selection and optimization presuppose that these entities already exist and that they have a function important for survival. New structures, however, may first appear on the scene without having any function.

Novelty often seems to arise “out of nowhere”, in spite of strong constraints that stabilize an existing structure. Innovation can be achieved without necessarily changing the genetic underpinnings of a feature, but by shifting the context and timing of their expression within the developmental sequence of an organism. This suggests that a feature’s integrity depends on a systemwide network of interactions involving other features.

The origin of biological novelty is tied to development (Wagner, 1994), the mechanisms by which an organism is constructed from genes and environmental inputs. Developmental processes generate and maintain nested levels of biological organization and therefore influence change at one level in response to change at its founding level.

A hypothetical example may help to illustrate the point.

The scenario is conventional: a mutation occurs, which results in a *new*₀ gene sequence coding for a *new*₁ protein whose interaction with the chemical machinery of the cell, set up by the remaining gene products, triggers a cascade of *new*₂ chemical reactions resulting in a *new*₃ signaling circuitry which enables the utilization of *new*₄ information.

Each time the word “new” denotes a different kind of novelty, because each time different kinds of constraints are in effect:

0. novelty₀: A sequence is a simple combinatorial object. At this level the generation of novelty is virtually unconstrained. If the sequence is

³Historically, the discussion about novelty in evolution runs under the headline of “homology”, the study of sameness (Fitch, 2000). Homology is the biological version of “prior-art”. An organismal feature is novel if it is not homologous to any feature in the ancestral species (Müller and Wagner, 1991). As with patent law, the meaning and the biological basis for homology are hotly debated. To replay this discussion in any serious way is beyond the scope of this essay, since it hinges on too much terminology.

sufficiently long, any random replacement of any symbol at any position yields a new_0 sequence. Novelty_0 is a throw of the dice.

1. novelty_1 : A protein is more than a sequence of symbols. It is a sequence that folds into a shape as a consequence of interactions between symbols along the chain. Three-dimensional space and the nature of intramolecular forces constrain which shapes are possible. At chemically relevant levels of resolution these constraints result in considerably fewer stable shapes than sequences. Not every novelty_0 is a novelty_1 .
2. novelty_2 : The shape of a molecule and the nature of chemical groups deployed by it define the molecule's "domain of interaction", that is, its capacity to participate in specific chemical action. Novelty_2 is a matter of chemistry.
3. novelty_3 : The constraints and opportunities of interaction within a given network of chemical pathways determine which new_3 network roles a new_2 molecular agent can participate in. How (or whether) a network forms or changes, depends on its molecular components, their interactions and kinetics. Novelty_3 is a network property.
4. novelty_4 : The innovated₃ network is characterized by its molecular components and their relationships. What is regarded, however, as new_4 "information" is a matter of the coupling between this network and other such networks either within the same, or between it and other, levels of biological organization. Indeed, it is the joint construction and maintenance of a chemical reality composed of a large number of linked networks which defines the biotic element of an environment. Novelty_4 is a property of a network of networks.

It is plain that novelty_4 cannot occur unless novelty_0 occurs. There is, however, a gap between novelty_0 and novelty_4 that theory is presently unable to bridge. We understand the possible for novelty_0 as the space of sequences over an alphabet. Yet we are unable to even specify the nature of the possible for novelty_4 . The problem is to understand the relation between *genotype*, the trivial level of novelty, and *phenotype*, the suite of organizational levels and associated behaviors generated by interactions among gene products. This relation is referred to as development. Here I use the word development to denote any processes that connect "vertically" two or more layers of biological organization.

Evolution is the conjunction of two factors: the selective amplification of genotypes based on the differential reproductive success conveyed by their phenotypes, and the modification of phenotypes through chance events at the level of genotypes. The theoretical agenda pertinent to the first factor aims at characterizing the conditions under which an innovation can, once generated, invade an existing population. The theoretical agenda pertinent to the second factor consists in understanding how novelty is generated in the first place – in other words, to understand the possible in biology by characterizing the routes along which one phenotype can be transformed into another. Virtually no theoretical framework exists to address the second agenda. Yet, without such a framework we cannot make sense of evolution, because we cannot understand its outcomes. To paraphrase Leo Buss, the hard task of evolutionary theory today is not to recognize an established innovation as advantageous in some fitness measure, but to understand how an innovation generates opportunities and constraints for subsequent innovations.

2 Some questions

The overall theme is to explore notions of organization at vastly different levels of abstraction and to understand innovation for each organizational class in response to change occurring at the level upon which that class is founded. The realm of molecular organization is the one where substantial theoretical progress is most likely to occur in this decade. Yet, the evolution (in some generalized sense) of functional, self-maintaining and homeostatic organizations is a central theme in many fields beyond biology proper, including many cognitive processes, as well as a diversity of human social and economic institutions. The origination and innovation of organization constitutes a “vertical question” cross-cutting chemistry, molecular biology, cognitive science, social science and economics. In all these disciplines the challenge is to (1) achieve a clear definition of organization as an autonomous individualized entity distinguished from mere aggregation, (2) understand how the robustness required for autonomy and individualization squares with evolvability, the capacity to be innovated, and plasticity, the capacity to be flexible and adaptive without losing identity, (3) understand the topology of the possible, that is, the routes by which organizations are transformed into new organizations, (4) understand what determines the possible.

Given a model of organization, that is, a model (or theory) of interacting objects that populate a founding level and a characterization of the organization(s) they give rise to, inquire into

Phenomenology: What constitutes novelty as opposed to variation? What are the kinds of organization and what are variations within each kind?

Variability: How does an organization change with respect to change at its founding level? If the founding level is combinatorial (for example, a sequence), the answer will be statistical in nature.

Control of variability: How does the architecture of an organization constrain and enable change? Once an organization has been generated, its structure will channel perturbations along definite directions. This structure involves network cycles (feedback), multiple pathways (redundancy), hierarchical and heterarchical layouts of networks, modularity. How do these aspects conspire to yield “axes” of resilience and vulnerability of an organization?

Evolution of variability: If the founding level also controls the mechanisms that generate organization, then change at the founding level may affect these very mechanisms. New organizational classes may become possible as a consequence. That which wasn’t possible before is a more radical form of novelty than that which didn’t exist before. In fact, major evolutionary innovations are innovations of development (Wagner and Altenberg, 1996).

Open endedness: Is open-ended evolution possible? What is required of a universe to be evolutionarily open-ended, that is, capable of generating ever new levels of organization?

In section 4 I will try to make some of these questions more concrete by describing examples – of varying maturity – taken from my own research.

3 From life to a technology of organization

Efforts to understand the nature of biological molecular organization, its architecture, the sources of its robustness and the routes along which it changes

are central to today's post-genomic molecular biology. Theory, modeling and experiment are getting closer, driven, at least partially, by the promise of biotechnology. In the light of this promise, the themes addressed here cannot be regarded as idle theorizing. Without a theoretical framework addressing the origin and innovation of (molecular) organization, we cannot hope to achieve anything that deserves the name of *biotechnology*, if technology means reducing the degree of empiricism in a practical art.

Why is this relevant to NASA?

One answer is "astrobiology". The search for life in the universe is a noble enterprise that touches many scientific, emotional and philosophical keys. Yet, it also has the taste of a clever sales trick to rally public (and, by extension, congressional) support for missions by flagging the prospect of elucidating the mysteries of life and its evolution. I think part of that is well taken and justified. The inroads into the mysteries of life and its evolution are, however, more likely to come in buckets from the massive efforts poured into understanding terrestrial life and the abstractions that follow from such understanding.

As I see it, the core civil mission of NASA is to explore space and get humankind into space. In the very long run, there is no reason why terrestrial life should be confined to this planet (and let's hope that we always have a choice). Of course, such an endeavour must be supported by many smaller near-term objectives of independent scientific and technological interest. What has biology to do with all that?

Design principles gleaned from molecular organization harbor the potential for new perspectives in technology – not just biotechnology. The capacity to construct artificial organizations that are robust in the sense of being self-repairing, self-maintaining, fault-tolerant and evolvable would be highly desirable. Yet, curiously, there exists no readily identifiable scientific tradition that seeks to understand what classes of such organizations are possible or to discover conditions necessary to achieve them.

Biology, computer science and engineering have a lot to say to each other, but that conversation has not yet begun in earnest. It requires environments in which this conversation is catalyzed and sustained. In his analysis of the golden age of high-energy physics, the Harvard historian Peter Galison points out the significance of CERN in Geneva as a place where theoreticians met not only experimentalists, but where both met a third tribe, the technicians

(Galison, 1997). Some of the major theoretical breakthroughs in elementary particle physics at CERN emerged from the interaction between engineers who were building detectors and the theoreticians who were inventing what there is to detect. From complete incomprehension first a pidgin and then a creole evolved that changed the theoreticians way of thinking⁴. The digression illustrates the importance of places where basic science meets technology to produce a use-inspired basic science (Stokes, 1997). Such environments are different in kind than those that served the *Endless Frontier* in the manner advocated by Vannevar Bush. NASA seems ideally positioned to become such an environment.

The technology needed for extending our reach into space might well be a “technology of organization”. Design principles underlying biological organization may be critical for achieving the distributed control and perception systems and the adaptive environments required to extend the scope of manned or unmanned space missions.

4 Research examples

I briefly introduce and review some items from my own research in an attempt to illustrate ways in which the scientific agenda outlined above can be approached. In compliance with Truth in Advertising I should point out that these examples are by no means exhaustive nor do they represent ultimate guidelines. They are what they are: examples.

In what follows the term “phenotype” can be liberally substituted with the term “organization”.

[1] **The folding of RNA sequences into secondary structures.** This is arguably the simplest, non-trivial, biophysically grounded instance of the novelty problem. The case is conceptually simple, because a formal character-

⁴In a similar vein, Galison emphasizes that the conception and development of relativity theory should be seen in conjunction with the towering technological problems of the time, which had to do with ... time: the synchronization of electrical clocks needed to operate the dramatically growing network of European railways (the time in Berlin used to differ arbitrarily from the time in Bern) and the problem of accurately establishing longitude to enable trade by sea between France and its colonies. In his Bern patent office, Einstein was exposed to the former environment, while Poincaré was the head of the French Bureau of Longitude.

ization of both the possible genotypes (sequences) and phenotypes (shapes) is available along with a reasonably transparent model of the mapping between the two. This enables a systematic exploration of the variation of phenotype with genotype. The primary goal is not the most accurate possible prediction of the shape into which a particular sequence folds, but rather a catalog of statistical characteristics of the relationship between sequence and structure. In a wider context, one would like to know how these characteristics interact with evolution and whether they can be expected to hold at higher levels of phenotypic complexity.

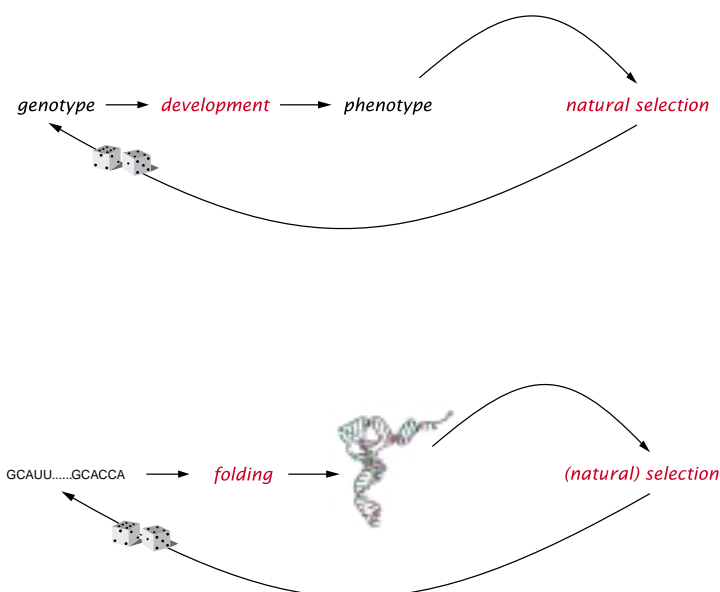


Figure 1: **The folding of RNA sequences into shapes as a proxy of a genotype-phenotype map.** Mutations occur at the genetic level. Their consequences at the phenotypic level are mediated by development, the suite of processes by which phenotype is constructed from genotype. RNA folding is a transparent and tractable model that captures this indirection of innovation within a single molecule. The RNA folding map is characterized by a number of remarkable statistical regularities with profound evolutionary consequences. It is plausible that these regularities generalize to more complex forms of development.

[2] **A formal abstraction of chemistry and a characterization of the self-maintaining production networks it generates.** Here I focus on networks of molecules that generate new molecules in chemical reactions. Leo Buss and I define as an “organization” a network that is self-maintaining.

The organization of such a network consists in the specific functional relationships between molecules that collectively ensure their continuous regeneration. The problem here consists in formalizing chemical reactions between molecules or, more generally, interactions between agents that result in the construction of new agents. This requires a theory linking the structure of

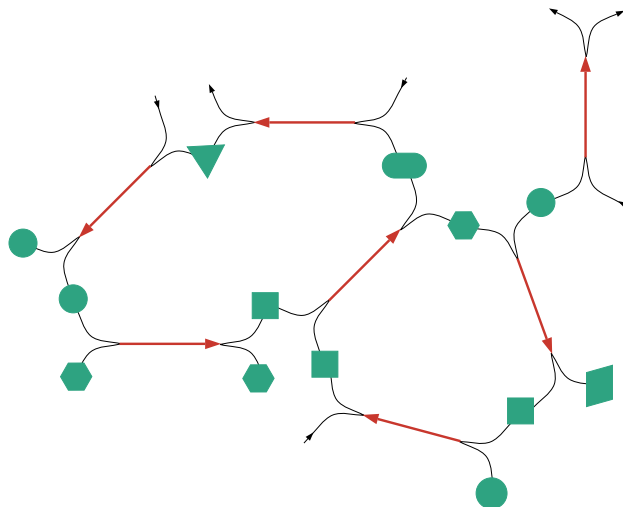


Figure 2: **Organization as a self-maintaining network of production pathways.** Molecules (represented by green shapes) react (red arrows) to generate new molecules that react to generate further molecules. In this way, an initial collection of molecules generates a network of chemical transformations. A reaction can be viewed in analogy to a logical inference or derivation: the reactants are premises and the products are conclusions which can be premises for further inferences. Leo Buss and I call “organizations” those networks that have become self-maintaining under conditions in which each molecule has a finite lifetime (because of an outflow or degradation).

agents to their behavior. In chemistry, the behavior of molecules consists in deterministically transforming the structure of those very molecules, thus yielding new behaviors. The feedback between agent structure which determines action and action targeted at agent structure generates, under appropriate boundary conditions, self-maintaining networks of production. The goal is to find and exploit a theory of such agents to characterize the networks they sustain. Ultimately, the question is: What is chemistry? Quantum mechanics answers that question by clarifying how chemistry arises from physics. Unfortunately, that answer does not clarify how molecular organization arises from chemistry. A different perspective on chemistry is needed, one that views molecules as grammatical entities encoding packets of action.

Such a view must yield tools for plugging these actions together and for analyzing the resulting network closures under a variety of boundary conditions.

[3] **Molecular signaling and the nature and behavior of distributed control networks.** Biological organization is more than a self-maintaining closure of chemical transformations. Organization also means control, that is, starting, stopping, synchronizing and sequencing concurrent processes whose coordination underlies behavior. Control and coordination within and be-

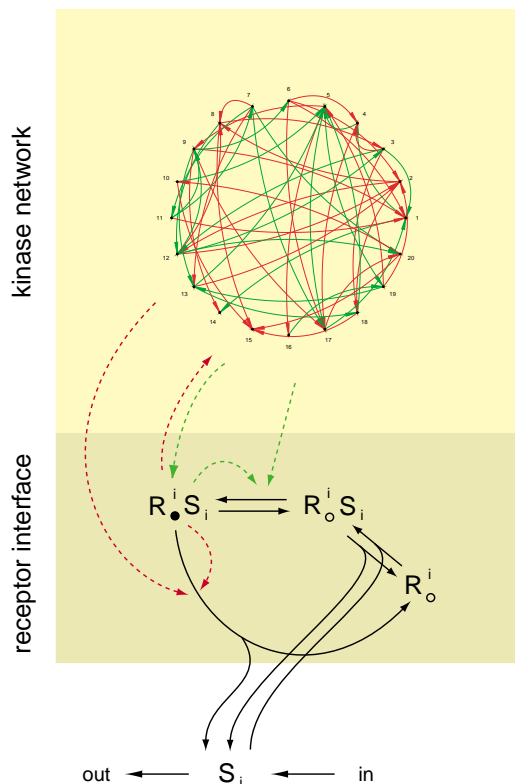


Figure 3: **Self-rewiring signaling networks.** The upper portion depicts a network of signaling proteins that activate (green) or deactivate (red) one another. The communication targets of each protein are controlled by the activation state of other proteins in the same network. Changes in that activation state cause the wiring diagram to change. The lower portion depicts the receptor interface that functions as an input to the network. Upon binding specific signals, receptors become activated and propagate the signal into the network. The gene expression layer has been omitted.

tween cells is achieved by molecular communication networks that transduce and relay signals typically originating with the binding of molecules to receptors located in the cell membrane. Communication here means the activation

or deactivation of a protein by another protein by transferring or removing a chemical token, such as a phosphate or methyl group. I want to explore molecular signal processing from a new angle by considering a network in which the communication links between components are not fixed, but controlled by the state of other components in the same network. This gives rise to a feedback between the network architecture and the activation kinetics induced on the network by that architecture. I further imagine a gene expression layer coupled to the network. By turning on and off genes that code for its own components, the network can control its own composition. The objective is to formulate a simple model system operating at three time scales with feedbacks among them: a short time scale at which the activation state of components changes, a medium time scale at which communication links change and a long time scale at which the very composition of the system is altered. I want to characterize the dynamical behavior of this class of systems, investigate their potential for learning and clarify the analogy to neural networks.

In the following I briefly elaborate on each project.

4.1 RNA folding and evolutionary dynamics: Evolution and development at the level of a single molecule

With my colleagues from Vienna, I used the computational folding of RNA sequences into minimum free energy secondary structures (henceforth shapes) as a simple biophysical toy-model of the mapping from genotype to phenotype⁵. The goal is to characterize the statistical features of this mapping and to understand their consequences for evolutionary dynamics (Schuster et al., 1994; Fontana and Schuster, 1998; Stadler et al., 2001).

The most important features are:

Typical shapes. There are many more sequences than shapes and shapes do not occur with the same frequency. In fact, a small fraction of shapes is realized significantly more often than others. These shapes are termed “typical” and they dominate the evolutionary process.

⁵The term “map” contains an important limitation: In this case, I’m not looking at the *process* by which genotype gives rise to phenotype. In RNA, the thermodynamic equilibrium secondary structure (phenotype) can be obtained from the sequence (genotype) without knowledge of the actual folding process. A kinetic model of folding, however, would be the appropriate analogue of development as a dynamic process.

Neutral networks. A sequence folding into a typical shape is characterized by a high degree of neutrality expressed as the fraction of one-error mutants (genetic neighbors) that retain that shape. Neutrality here means equivalence with regard to shape. The same holds for these neighbors. In this way, jumping from neighbor to neighbor, we can map an extensive mutationally connected network of sequences that fold into the same shape. We termed such networks “neutral networks”. A neutral network expresses the stability of a phenotype against genetic mutations. Yet, it also enables phenotypic change to occur. Consider an evolving population whose currently best phenotype is shape A . Suppose further that shape B is the better phenotype, but that it can’t be accessed by a small (and hence probable) mutation from the population’s current location in genetic space. The population, however, is not stuck. Because of connected neutrality, the population can drift in genetic space while preserving the currently best phenotype until it eventually comes close to sequences that fold into the better shape B . The significance of neutrality consists, therefore, in enabling the preparation of a genetic context in which a subsequent mutation becomes phenotypically consequential. Phenotypic change appears suddenly, but the underlying genetic make-up changes all the time. When a population drifts over a neutral network, the phenotype does not change, but the potential for change changes.

Shape space covering. Neutral networks should be imagined as high-dimensional sponges that are heavily entangled with one another. In fact, they are so much intertwined that all typical shapes are realized within a small neighborhood (compared to sequence length) of any random sequence. For example, for sequences of length 100, at least one instance of every typical shape is, on average, no more than 15 mutations away from any random sequence.

The Topology of the Possible: ‘A is near B’ does not imply ‘B is near A’

Neutral networks have a straightforward, yet subtle, consequence. The adjacency of one neutral network to another in sequence space, expressed as the relative size of shared boundary, defines a relationship of accessibility among phenotypes. This can be used to construct a space that reflects how likely one phenotype appears as an innovation of the other by genetic mutation. The formal structure of that space is a pre-topology, a rather unfamiliar animal. The main point is that for RNA this space lacks a notion of distance, because nearness understood as accessibility is not symmetric. The reason

is that neutral networks can differ vastly in size. Shape B may be easily accessible by genetic mutation from shape A without the reverse being true. Think of the United States in terms of such a boundary topology: Pennsylvania is near New Jersey, but New Jersey is not near Pennsylvania, since a random step out of NJ is likely to end up in PA, but not *vice versa*.

The genotype-phenotype map (that is, development) induces the topological structure of phenotype space by determining the evolutionary routes along which phenotype B can be obtained from phenotype A . This is quite different from the traditional image of phenotype space as a highly regular metric space constructed around a notion of similarity (morphological or other) between phenotypes. Punctuated equilibria, constraints to variation and irreversibility in evolution become immediately intelligible in this new space, its unfamiliar structure notwithstanding.

The conceptual position developed here is, historically, not a new one. It has been expressed informally by many biologists since the beginning of the 20th century. The RNA model simply provides a concrete mechanistic illustration that places the discussion within a framework of formal theory (in which, for example, notions like continuity and discontinuity of evolutionary trajectories and the genotype-phenotype map can be made precise) rather than leaving it to confusion generated by incommensurate interpretations and people arguing at cross purposes.

Our theory motivated Eric Schultes and David Bartel from the Whitehead Institute to a beautiful RNA experiment reported in the journal *Science* (Schultes and Bartel, 2000). The experiment provides strong evidence for the existence of neutral networks and shape space covering.

Plasticity mirrors Variability ... and the Origin of Modularity

Lauren Ancel and I have recently extended the notion of RNA phenotype to include phenotypic plasticity (Ancel and Fontana, 2000). Plasticity means that a given genotype provides several alternative phenotypes to an individual⁶. In the simple case of RNA, plasticity means that the phenotype is no longer just the minimum free energy shape (ground state), but rather the set of alternative shapes in the energetic vicinity of the ground state. Thermal fluctuations cause the molecule to wiggle among these alternative shapes.

⁶An example of a mechanism that generates plasticity in higher organisms is learning, whose capacity is genetically influenced.

Analysis of the plastic genotype-phenotype map led to the discovery of a further statistical feature with evolutionary consequences. First, there is a positive correlation between plasticity (alternative shapes available to a single sequence) and variability (the degree to which new shapes can be generated by mutating that sequence). Second, the set of ground states realized in the genetic vicinity of a sequence is typically a subset of the plastic repertoire of that sequence.

These findings are a consequence of one and the same mechanism underlying different phenotypic features (here plasticity and variability). Because of this coupling, selection acting on one feature also affects the other. In computer simulations we found that selection for highly stable ground states (low plasticity) dramatically reduces genetic variability – even to the point of grinding evolution to a halt, because of insufficient variation. However, we also found that low-plasticity shapes are modular, consisting of kinetically, thermodynamically and genetically autonomous pieces of shape. A selection regime for low plasticity therefore drives the population into an evolutionary trap with respect to point mutations as the source of variation. Yet, curiously, this trap has precisely the necessary structural organization to eliminate itself by enabling a new source of variation through the shuffling of modules.

4.2 Abstract Chemistry: Organization as a self-maintaining network of transformations

Leo Buss (Yale) and I have written extensively about the motivation underlying this project (Fontana and Buss, 1994a,b, 1996): Biology lacks a theory of the possible, because it lacks a theory of organization. What do we mean by organization? We mean a self-maintaining system of molecular transformations. This, of course, is not all there is to the notion of organization, but it constitutes one fundamental aspect. How can it be formalized? Our answer was to seek a formal level of abstraction for chemistry that emphasized molecules as agents of transformation, to define a population dynamics of such agents that would yield self-maintaining ensembles as fixed-“points” and to characterize these ensembles as kinetically persistent algebraic structures.

In chemistry, molecules combine and interact by transforming one another into further molecules. In mathematics, a theory of transformations is given by λ -calculus, a formal language that provides a notation and rules to express

functions that act on the very expressions representing them. The significance of λ -calculus derives from the mathematical meaning of its rules. This is best conveyed by a variant of λ -calculus in which expressions also possess an abstract “shape”, known as type, that constrains who can interact with whom⁷. It is well-known in logic that λ -calculus corresponds to a theory of proofs. In this correspondence, a type stands for a logical proposition and a λ -expression of that type represents a proof of that proposition. The rules of transformation correspond to the rules of logical inference. To the extent that λ -calculus abstracts an essential aspect of chemistry, we are led to a new perspective on chemistry. At one level of description, a molecule is a quantum mechanical entity. Yet, at another level, a molecule may be the proof of a logical proposition which we call its shape⁸. The synthesis of a molecule is like proving a theorem by using lemmas (other molecules) according to rules of a symbolic logic yet to be formalized. A self-maintaining system of theorems that mutually prove one another, feeding on axioms, is what logicians call a “theory” – and biologists call a metabolism.

Buss and I pursued this idea by implementing a computer model of a well-stirred stochastic flow reactor aimed at exploring the generic behavior of many applicatively interacting λ -expressions. This constructive dynamical system indeed converges on self-maintaining networks of transformation characterized by syntactical and functional invariances, a capacity for self-repair upon removal of network components, strong constraints to network extension upon the addition of new expressions, and a “center”, defined as the smallest kinetically persistent and self-maintaining generator set of the network. Such networks we called “organizations”. The invariances underlying these organizations permit their abstract description as algebras, independently of their concrete instantiation in λ -calculus. Imposition of different boundary conditions on the stochastic flow reactor generates different levels of organization, and a diversity of organizations within each level. Level 0 is defined by self-copying expressions or simple ensembles of copying expressions. Level 1 denotes self-maintaining organizations in the above sense, and Level 2 is defined by self-maintaining metaorganizations composed of Level 1 organizations.

⁷For example, computer-representations of numbers (numerals) come in different basic shapes, such as “integer” or “float”. These abstract shapes control which functions can act on these numerals.

⁸This is less far fetched than it seems at first glance. In fact, a good chemist reads a molecular shape as a statement about the potential actions of that molecule.

The wealth of phenomena generated by this simple abstraction of chemistry and the prospect of a formal framework to describe them, encouraged us to seek modifications of extant logics and calculi in an attempt to move closer to the chemistry we know. So far we have not succeeded in a mathematically meaningful way. I continue, however, to seek ways of reviving this project along with applications to other domains, since the idea of organization as a self-sustaining network of transformations is hardly unique to chemistry.

Historically, this project is an ambitious extension of the “autocatalysis” and “autopoiesis” themes pioneered by Francisco Varela (Maturana and Varela, 1980), Stuart Kauffman (Kauffman, 1993), Norman Packard, Doyne Farmer (Farmer et al., 1982) and Otto Rössler. It is ambitious in that it imputes an analogy between the structure of logic and chemistry. It is an extension in that it plays with these themes at the level of abstract functional ensembles.

4.3 Self-rewiring signaling networks: Organization as distributed control

In the near term I will focus on the structure, function and evolution of distributed combinatorial control networks. The networks I have in mind are primarily molecular, in particular intra- and intercellular signal transduction networks⁹.

Is there a network paradigm underlying molecular signaling networks? I believe so and decided to focus in particular on one putative aspects of signaling and their consequences: self-rewiring.

Some signaling components are able to redefine with whom another component of the same network is communicating with. This means that the architecture or topology of the network is dynamic and (at least in part) controlled by the network state (the concentration vector) itself. A signaling component (such as a kinase) is here defined in terms of a repertoire of possible downstream targets (within the same network) that it *can* interact with. Yet, which of these interactions actually *do* occur at a given time t , is controlled by the concentration of other signaling components. This generates a feedback loop between the network architecture and the dynamics induced by it: a particular network topology determines the concentration

⁹Many issues, however, are similar to those arising in emerging technologies, such as the peer-to-peer device control networks pioneered by Echelon Corporation, www.echelon.com.

changes of network components which, in turn, rewire the network topology. In a system of this kind, a fixed pool of components represents a variety of *possible* control networks from which a particular one is induced in response to an external signal.

The obvious resemblance of this scheme to neural networks¹⁰ suggests to investigate the learning capabilities of self-rewiring control networks. Learning is, perhaps, the construction of memory or at least a history-dependent long-term modification of parameters governing a dynamical system. If self-rewiring signaling systems do learn, they should respond in a characteristic fashion to the re-presentation of a signal to which they have been exposed before (memory) or they should trigger long-term architectural changes in response to it. The latter may simply require the addition of a gene expression layer to the model. If genes coding for the components of a network are among the targets controlled by that same network, long-term endogenous architectural changes, such as the removal of nodes (“knock-outs”) or the addition of nodes (“knock-ins”), become possible.

In a first approach, the network dynamics is modeled in terms of mass-action kinetics. This may be appropriate for some portions of a signaling network, but hardly for the whole network. The overall behavior of many control networks depends on single events, such as checkpoints. These are not meaningfully described by traditional kinetics, but emphasize logical aspects of behavior. Building a unified framework for kinetics and logic is a significant challenge that must be met for understanding cellular control networks.

¹⁰There are, of course, differences with regard to kinetics. Moreover, in molecular signaling, a communication channel is established by direct physical contact and recognition between the molecules. The number of shapes any molecular shape can recognize are limited to a few. In neural signaling, a communication channel is established by connecting two neurons with a “wire”, and a wire can connect arbitrary neurons.

References

- L. AnceI and W. Fontana. Plasticity, evolvability and modularity in RNA. *J. of Exp. Zoology (Molecular and Developmental Evolution)*, 288:242–283, 2000.
- J. D. Farmer, S. A. Kauffman, and N. H. Packard. Autocatalytic replication of polymers. *Physica D*, 22:50–67, 1982.
- W. M. Fitch. Homology, a personal view on some of the problems. *Trends in Genetics*, 16:227–231, 2000.
- W. Fontana and L. W. Buss. ‘The arrival of the fittest’: Toward a theory of biological organization. *Bull. Math. Biol.*, 56:1–64, 1994a.
- W. Fontana and L. W. Buss. What would be conserved ‘if the tape were played twice’. *Proc. Natl. Acad. Sci. USA*, 91:757–761, 1994b.
- W. Fontana and L. W. Buss. The barrier of objects: From dynamical systems to bounded organizations. In J. Casti and A. Karlqvist, editors, *Barriers and Boundaries*, pages 56–116. Addison-Wesley, Reading, MA, 1996.
- W. Fontana and P. Schuster. Continuity in Evolution: On the Nature of Transitions. *Science*, 280:1451–1455, 1998.
- P. L. Galison. *Image and Logic: A Material Culture of Microphysics*. University of Chicago Press, Chicago, 1997.
- S. A. Kauffman. *The origins of order*. Oxford University Press, New York., 1993.
- H. Maturana and F. J. Varela. *Autopoiesis and Cognition: The Realization of the Living*. D. Reidel, Boston, 1980.
- G. B. Müller and G. P. Wagner. Novelty in evolution: Restructuring the concept. *Annu. Rev. Ecol. Syst.*, 22:229–256, 1991.
- E. A. Schultes and D. P. Bartel. One sequence, two ribozymes: Implications for the emergence of new ribozyme folds. *Science*, 289:448–452, 2000.
- P. Schuster, W. Fontana, P. F. Stadler, and I. Hofacker. From sequences to shapes and back: A case study in RNA secondary structures. *Proc. Roy. Soc. (London) B*, 255:279–284, 1994.

- B. M. R. Stadler, P. F. Stadler, G. Wagner, and W. Fontana. The topology of the possible: Formal spaces underlying patterns of evolutionary change. *Journal of Theoretical Biology*, in press, 2001.
- D. E. Stokes. *Pasteur's Quadrant: Basic Science and Technological Innovation*. Brookings Institution Press, Washington D.C., 1997.
- G. P. Wagner. Homology and the mechanisms of development. In B. K. Hall, editor, *Homology: The Hierarchical Basis of Comparative Biology*, pages 273–299. Academic Press, San Diego, California, 1994.
- G. P. Wagner and L. Altenberg. Complex adaptations and the evolution of evolvability. *Evolution*, 50:967–976, 1996.