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ORIGINAL PAPER

Explications of Functional Entailment in Relational Pathophysiology

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Abstract I explicate how various relational interactions between (M,R)-systems may have realizations in pathophysiology, and how the possible reversals of the effects of these interactions then become therapeutic models. Functional entailment receives a rigorous category-theoretic treatment, and plays a crucial role in this continuing saga of relational biology.

Keywords Relational biology · Functional entailment · (M,R)-systems · Pathophysiology · Therapeutics

1 Prerequisites

This paper is a sequel to a continuing sequence of papers on relational biology published in this journal: Louie (2006), (2008), (2010), Louie and Kercel (2007). From these earlier papers, I shall adopt the notation and terminology and draw upon results. For a more detailed exposition, the enthused reader may find a comprehensive introduction to relational biology in my book *More Than Life Itself: A Synthetic Continuation in Relational Biology* (Louie 2009). Since I shall be referring to this book many times, I shall henceforth use the canonical symbol *ML* in its stead. In this paper, when various topics are encountered, when appropriate I shall refer the reader to relevant passages in *ML* for further exploration. A recent special topical issue of this journal (*Axiomathes*, volume 21 number 3, 2011) comprises four essays commenting on *ML* and my responses (Louie 2011) to these comments.

I assume the reader is already familiar with the premises of the Rashevsky-Rosen school of relational biology. If not, I cordially invite the reader to review the references cited above before continuing. At the expense of self-containment, such

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prerequisites are instituted by necessity; else, if I were to offer a recapitulation of 'previously on relational biology' for every paper in succession, the lengths of the papers would monotonically increase in a Fibonacci sequence! In particular, as prerequisites the reader should have already understood the following statements.

Definition The entailment of an efficient cause is called *functional entailment*. (*Cf. ML*: Section 5.15)

Definition A natural system is *closed to efficient causation* if its every efficient cause is (functionally) entailed within the system. (*ML*: 6.23)

Postulate of Life A natural system is an *organism* if and only if it realizes an (M,R)-system. (*ML*: 11.28)

Theorem *A natural system is an organism if and only if it is closed to efficient causation.* (*ML*: 11.29)

This sequence of statements is a succinct summary of our answer to the "What Is Life?" question. One sees that the defining characteristic of a living system (i.e., 'organism' in its most general sense), 'closure to efficient causation', anchors on the key concept of 'functional entailment'. In this paper, I shall first present a new description in category-theoretic language of this key concept. (So I am after all giving a précis of 'the story so far' on this one special topic, although the emphasis of this alternate description is on the formal setting of the representation.) Then, I shall explicate how variations in functional entailment patterns are realized in pathophysiology in relational-biologic terms.

2 The Logic of Entailment

In common usage, the verb 'to *entail*' means 'to have as an inevitable *accompaniment*' or 'to involve unavoidably'. In logic, the usage is tightened to explicitly involve inference, whence 'to entail' means 'to necessitate as a *consequence*'. That the logical usage of 'entailment' in the consequential sense is more stringent than its common usage in the concomitant sense is concisely expressed in the cliché "Correlation does not imply causation."

If A entails B (whatever entities A and B are), then it is denoted

$$A \vdash B. \tag{1}$$

The *entailment symbol* $\vdash$ is called 'right tack' in Unicode, and has also taken on the ideographic name 'turnstile'. It is used in various branches of mathematics, but in all contexts it invariably has the logical meaning that one thing follows another as a necessary consequence.

In the predicate calculus of formal logic, entailment appears in the *conditional statement*

$$p \rightarrow q; \tag{2}$$

'If p, then q.' The antecedent p whence *entails* the consequent q:

$$p \vdash q, \tag{3}$$

and this *inferential entailment* is called a *syntactic consequence*. It is independent of any *interpretation* within the formal system under consideration; i.e., logical statement (3) is simply a string of symbols for which the *meaning* or *validity* is irrelevant.

If the conditional statement (2) is *true*, then it becomes the *implication*

$$p \Rightarrow q; \tag{4}$$

'p implies q.' The entailment is then denoted

$$p \models q, \tag{5}$$

and is called a *semantic consequence*. This happens when *no interpretation* within the formal system makes p true and q false (which is the only combination that renders the conditional statement (2) *false*). When q is a semantic consequence of p, in the parlance of *model theory* in logic one says "*q models p*". The *modelling symbol* $\models$ is, naturally, also ideographically called 'double turnstile'.

Incidentally, the difference between statements (2) and (4) [and between statements (3) and (5)] illustrates the contention of *infer* versus *imply* in their logical sense. To infer in an inference (as in statements (2) and (3)) is syntactic; to imply in an implication (as in statements (4) and (5)) is semantic. This distinction agrees with the words' common usage (which is, alas, often mistakenly executed). To infer is to deduce or conclude from facts and reasoning, but there is possibly a certain amount of 'guesswork' (whence feasibly 'error') involved. To imply is to strongly suggest the truth or existence of (a thing that may not be expressly asserted). In communications, the *sender* of a message *implies* by putting a suggestion into the message, and the *receiver infers* by taking a suggestion (not necessarily the same one, whence miscommunication) out of the message. The difference between imply and infer is thus in the degree of certainty, the extent of relative truth.

3 Causality and Inference

One may declare that both science and mathematics are in their different ways concerned with systems of *entailment*. Aristotelian analysis can be applied to any entailment structure, simply by (as Aristotle did) asking "why?" about it. Statement (1) of 'entailment in the abstract' is realized as causal entailment in the natural world, and inferential entailment in the formal world.

Causality is the principle that *everything has a cause*. *Inference* is the forming of conclusion from premises, the finalization of a proposition as a necessary consequence, in short, 'entailment'. Indeed, the Latin words for entail and infer have the same stem: entail is *adferre* and infer is *inferre* (literally 'to bring to' and 'to bring in', but essentially interchangeable).

It is important to note that I am using the word 'cause' in the *Aristotelian* sense, i.e., 'grounds or forms of explanation', *explanatio* (ML: 5.2). This *includes* (but is more expansive than) the common-usage sense of causality as the relation of cause

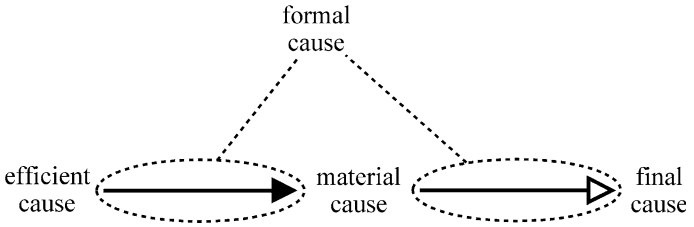
and effect. The realizations of entailment as inference in the formal world and Aristotelian causality in the natural world are exactly analogous, both incarnated in the conditional statement (2). When $p \rightarrow q$ and given p, one may *formally infer* q, and *naturally* q is *enabled*. *Enablement* is the *endowment* of the *means* to be or to do, 'making possible', and is verily Aristotle's $\alpha\check{\iota}\tau\iota o\nu$. Our contemporary notion of 'cause', as 'that which produces an effect', has a sense of *fait accompli*. 'Causation' in this modern sense is the act of causing *and* the act of producing an effect, so it has restrictively evaluated the conditional statement (2) into the implication (4). Aristotle's cause is *potentiality*, which provides the means but does not necessarily have to (although it may) be 'committed' into the modern 'cause' that is *actuality*. For another synthesis on potentiality versus actuality, in terms of contextual entailment versus realized entailment, the reader may refer to Kineman (2011).

In Section 4.15 of *ML*, I wrote (referring to Natural Law)

> This equivalence of causality in the natural domain and inference in the formal domain is an epistemological principle, the axiom
>
> *Every process is a mapping*.
>
> Just like the axiom "Everything is a set." leads to the identification of a natural system N and its representation as a set (*cf.* 4.4), mathematical equations representing causal patterns of natural processes are results of the identification of entailment arrows and their representations as mappings.

What the two axioms "Everything is a set." and "Every process is a mapping." say is that we, in the Rashevsky–Rosen school of relational biology, take implicitly as the mathematical foundation of our science the category **Set**, in which sets are **Set**-objects and mappings are **Set**-morphisms. By extension, we may also consider concretizable categories **C** (which are equipped with faithful functors from **C** to **Set**).

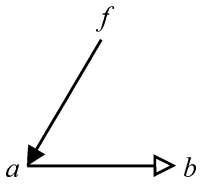
In particular, we consider entailment the central concept in relational biology (as it is in the entire scientific enterprise and beyond), and the Aristotelian analysis of entailment is comprehensively modelled in terms of its manifestations on a mapping. The embedding of the four causes as components of the relational diagram of a mapping is succinctly summarized in



(6)

I have explained this anatomy in several of my previous publications (e.g., Chapter 5 of *ML*) and will not elaborate on it here.

When a *mapping* $f : A \rightarrow B$ is represented in the element-chasing version $f : a \mapsto b$, its relational diagram in graph-theoretic form may be drawn as



(7)

The hollow-headed arrow denotes the *flow* from *input* $a \in A$ to *output* $b \in B$, and the solid-headed arrow denotes the induction of or constraint upon this flow by the *processor f*. The processor and output relationship may be characterized '*f entails b*', which may then be denoted as

$$f \vdash b. \tag{8}$$

Note that the processor *f* is *that which entails*, and the output (effect) *b* is *that which is entailed*. Because of the location of the symbols with respect to the arrows, 'that which entails' may be identified with the (*tail of the*) *solid-headed arrow*, and 'that which is entailed' may be identified with the (*head of the*) *hollow-headed arrow*. Stated otherwise, if something *entails*, then it needs to *initiate a solid-headed arrow*; if something *is entailed*, then it needs to *terminate a hollow-headed arrow*.
The final cause (output or effect $b \in B$) of a mapping *f* is, therefore, entailed by the efficient cause (the processor itself) of *f* by definition. In other words, 'that which entails' is always the efficient cause, and a process always entails its *own* output as final cause; whenever there is entailment, final causes are entailed. Thus the phrases 'final-cause entailment' and 'closure to final causation' are redundancies.

It is when 'that which is entailed' has a *dual role*, an alternate description as some entity in addition to being final cause of its own mapping, that the situation becomes even more interesting. This happens when two processes interact, and is modelled by two mappings *in composition*.

4 Sequential Composition from a Category-Theoretic Standpoint

Sequential composition is an integral part of the definition of a category. In a category **C**, (sequential) *composition* $\circ$ is a requisite mapping: for any three **C**-objects *A*, *B*, *X*,

$$\circ : \mathbf{C}(A, X) \times \mathbf{C}(X, B) \rightarrow \mathbf{C}(A, B), \tag{9}$$

takes $g : A \rightarrow X$ and $h : X \rightarrow B$ to its *composite* $f = h \circ g : A \rightarrow B$.

Composition $\circ$ may be considered a binary operation that takes a pair of **C**-morphisms to a **C**-morphism:

$$\circ : (g, h) \mapsto f. \tag{10}$$

In particular, one may note from its entailment pattern (10) that sequential composition in a category **C** is evidently not generally *itself* a **C**-morphism. It is also

important to note that the binary operation $\circ$ is *not* defined for *all* pairs of **C**-morphisms: *the codomain of the first argument g must be identical to the domain of the second argument h* (the common **C**-object X in definition (9)) for the binary operation to proceed. The two arguments have to share a 'common middle', as it were.

Although the **C**-morphisms may not necessarily be mappings, composition *itself* is a mapping (from a set to a set). This is because, for each pair of **C**-objects A and B, the *hom-set* of **C**-morphisms $\mathbf{C}(A,B)$ is above all a *set*, in any category **C** (whether concretizable or not; roughly, whether it is a category of 'sets with structure' or not), Thus the category **Set** involves itself in an essential way in *every* category. The domain of $\circ$ is a union of Cartesian product of hom-sets over pairs that share a 'common middle'

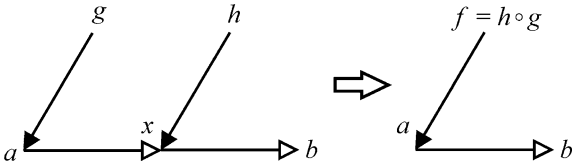
$$\mathrm{dom}(\circ) = \bigcup_{A,B,X} \mathbf{C}(A,X) \times \mathbf{C}(X,B); \tag{11}$$

its codomain is the union of all the hom-sets of **C**

$$\mathrm{cod}(\circ) = \bigcup_{A,B} \mathbf{C}(A,B) \tag{12}$$

(where A, B, X range over all **C**-objects).

When $\mathbf{C} = \mathbf{Set}$ and when sequential composition is presented as an element-chasing relational diagram (where, naturally, $a \in A$, $b \in B$, and $x \in X$), one has



(13)

with corresponding entailment diagram

$$g \vdash x,\ h \vdash b \ \Rightarrow\ f = h \circ g \vdash b. \tag{14}$$

The sequential composite $f = h \circ g$ entails the (final) final cause b. The 'common middle' element $x \in X$ is entailed as the final cause of its own processor g, and it is also relayed as the *material cause* of the next processor h; *the final cause of g is the material cause of h*. It is this *second role* of the 'relayed element' $x \in X$ that is remarkable (in the sense of 'worthy of a remark', i.e., 'worth naming') in sequential composition, whence called *material entailment*.

5 Sequential Chain and Sequential Cycle

When three **C**-morphisms have appropriate 'common relays', their sequential compositions may be defined, indeed, sequentially. Explicitly, if $f : A \to B$, $g : B \to C$, $h : C \to D$, then both $h \circ (g \circ f)$ and $(h \circ g) \circ f$ are defined. It is an axiom in category theory that composition is *associative* (*ML*: A.1), whence $h \circ (g \circ f) = (h \circ g) \circ f$.

Thus the (triple) composite may be denoted unambiguously without brackets, $h \circ g \circ f : A \to D$.

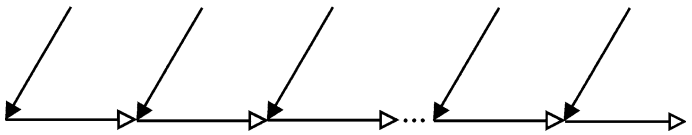
Sequential composition can clearly be extended to any finite number of **C**-morphisms. If

$$f_i : X_i \to X_{i+1}, \quad i = 0, 1, \ldots, n-1, \tag{15}$$

then their composite is

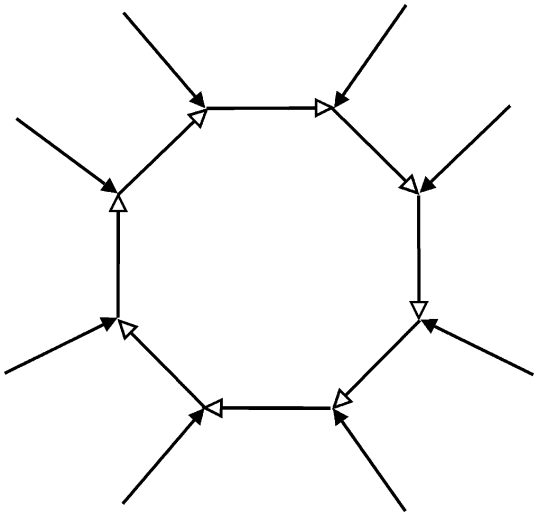
$$f_{n-1} \circ f_{n-2} \circ \cdots \circ f_1 \circ f_0 : X_0 \to X_n. \tag{16}$$

For mappings, when represented in relational diagram in graph-theoretic form, the composite is the *sequential chain*



(17)

If $X_n = X_0$, then the chain folds into a cycle:



(18)

(shown for $n = 8$, for graphical convenience). Note that within this *sequential cycle*, the arrows involved have a consistent direction, and are *all hollow-headed* (with solid-headed arrows peripheral to the cycle). That is, the compositions involved in the closed path are all sequential, and each final cause has the additional role of being the material cause of the subsequent mapping. A sequential cycle is, therefore, called a *closed path of material causation*.

The sequential composite $f_{n-1} \circ f_{n-2} \circ \cdots \circ f_1 \circ f_0 : X_0 \to X_0$ may, depending on the emphasis, be interpreted as the automorphism

$$x \mapsto f_{n-1} \circ f_{n-2} \circ \cdots \circ f_1 \circ f_0(x), \tag{19}$$

the *identity mapping*

$$f_{n-1} \circ f_{n-2} \circ \cdots \circ f_1 \circ f_0 = 1_{X_0} \in H(X_0, X_0), \tag{20}$$

or the *fixed point* $c \in X_0$ of the mapping $f_{n-1} \circ f_{n-2} \circ \cdots \circ f_1 \circ f_0$,

$$f_{n-1} \circ f_{n-2} \circ \cdots \circ f_1 \circ f_0(c) = c. \tag{21}$$

Note that, because of the cyclic nature of the compositions involved in a sequential cycle, corresponding interpretations apply to all the n composites of the cyclic permutations of the mappings

$$f_{i-1} \circ f_{i-2} \circ \cdots \circ f_0 \circ f_{n-1} \circ \cdots \circ f_{i+1} \circ f_i \in H(X_i, X_i) \tag{22}$$

for $i = 0, 1, \ldots, n-1$ (with the natural *modulo n* congruence of the subscript i).

6 Exponential, Hierarchical Composition, and Functional Entailment

If a category $\mathbf{C}$ has (binary) products, then there is an induced functor $\cdot \times \cdot : \mathbf{C} \times \mathbf{C} \to \mathbf{C}$. In particular, fixing a $\mathbf{C}$-object Y, consider the induced functor $\cdot \times Y : \mathbf{C} \to \mathbf{C}$ that maps $\mathbf{C}$-objects $X \mapsto X \times Y$. Then, by definition (*ML*: A.48), this functor $\cdot \times Y : \mathbf{C} \to \mathbf{C}$ has a *right adjoint* $G : \mathbf{C} \to \mathbf{C}$ (which clearly depends on Y) if and only if one has the natural isomorphism $\varphi : \mathbf{C}(X \times Y, Z) \cong \mathbf{C}(X, GZ)$. If one denotes this right adjoint $G(\cdot) = (\cdot)^Y$, then

$$\mathbf{C}(X \times Y, Z) \cong \mathbf{C}\left(X, Z^Y\right). \tag{23}$$

The $\mathbf{C}$-object Z^Y is called an *exponential* (*ML*: A.52). Specifying the adjunction $\left\langle \cdot \times Y, (\cdot)^Y, \varphi \right\rangle : \mathbf{C} \to \mathbf{C}$ amounts to assigning to each pair of $\mathbf{C}$-objects X and Z the $\mathbf{C}$-morphism $e : Z^X \times X \to Z$, called the *evaluation morphism*, which is natural in Z and universal from $\cdot \times X$ to Z. (*Cf. ML*: A.53 on cartesian closed category).

In the category **Set**,

1. the exponential Z^Y is the hom-set $\mathbf{Set}(Y, Z)$ of all mappings from Y to Z;
2. $Z^Y \times Y^X \to Z^X$ is a natural transformation, which agrees with (sequential) composition of mappings (cf. definition (9));
3. the evaluation mapping $e : Z^X \times X \to Z$ is $e : (g, x) \mapsto g(x)$ for $g : X \to Z$ and $x \in X$.

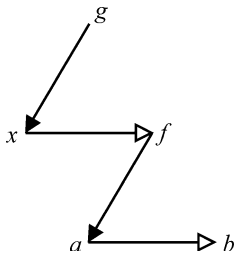
Note that, in a general category, given $\mathbf{C}$-objects Z and Y, the exponential Z^Y does not necessarily exist. Even when it does exist, it is simply a $\mathbf{C}$-object; it does not necessarily correspond to the hom-set $\mathbf{C}(Y, Z)$. This is (roughly) because there is not always a 'good' way to define a $\mathbf{C}$-structure on the hom-set $\mathbf{C}(Y, Z)$ to turn it into a $\mathbf{C}$-object.

In a category $\mathbf{C}$ in which exponentials exist *and* they correspond to hom-sets (an example is, of course, **Set**), a composition that is different in kind from sequential composition may be defined. This is called *hierarchical composition*, embodied in the natural isomorphism

$$\mathbf{C}\left(X, B^A\right) \cong H(X, H(A, B)), \tag{24}$$

through which a **C**-morphism $g \in \mathbf{C}(X, B^A)$ may be interpreted as a mapping (i.e., **Set**-morphism) $g \in H(X, H(A, B))$ (where I have used the hom-set notation $H(Y, Z)$ for a *subset* of the set $\mathbf{Set}(Y, Z) = Z^Y$ of *all* mappings from set Y to set Z).

The codomain $H(A, B)$ of $g \in H(X, H(A, B))$ is a collection of mappings: for $x \in X$, $f = g(x) : A \to B$. Since *the codomain of g contains f* (i.e., $f \in H(A, B)$), the mapping g may be considered to occupy a higher 'hierarchical level' than the mapping f. Let the element chases be $f : a \mapsto b$ and $g : x \mapsto f$. Then one has the relational diagram



(25)

with the corresponding composition of entailment diagrams

$$g \vdash f, f \vdash b \Rightarrow g \vdash f \vdash b. \tag{26}$$

The 'common middle' here is the mapping $f \in H(A, B)$: *the final cause of g is the efficient cause of f*. What is relayed, that which the first mapping entails, is now the *processor* of the next mapping; i.e. the dual role of the first final cause is that of the next efficient cause. This different mode of entailment, the *entailment of an efficient cause*, is given the name of *functional entailment*, and may be denoted succinctly

$$\vdash f. \tag{27}$$

Because of the natural isomorphism

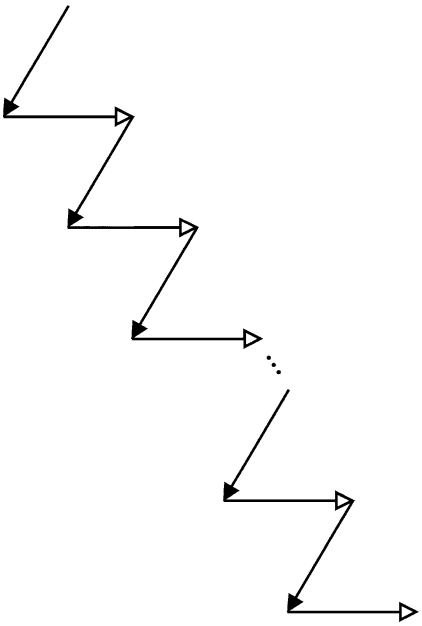
$$H(X \times A, B) \cong H(X, H(A, B)) \tag{28}$$

(consequence of (23) and (24)), a mapping $g \in H(X, H(A, B))$ that entails another mapping and has a hom-set as codomain may be considered equivalently as the isomorphic $g \in H(X \times A, B)$ that has a simple set as codomain. Thus one sees that, while hierarchical composition is *formally* different from sequential composition (as is evident from a comparison of the entailment chains (14) and (26)), functional entailment is not *categorically* different. This isomorphic resolution (28) of the entailment of an efficient cause has important biological explications, as we shall see presently.

7 Hierarchical Chain and Hierarchical Cycle

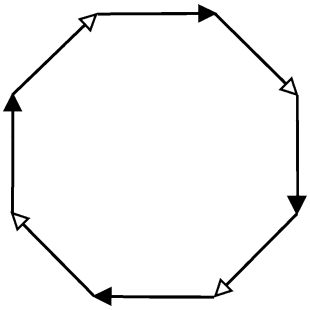
Since in the functional entailment $g \vdash f$, the final cause (i.e. output) of g is the efficient cause of f, the mapping g may be considered an 'efficient cause of efficient

cause'. An iteration of efficient causes is inherently hierarchical, in the sense that a lower-level efficient cause is contained within a higher-level efficient cause. Similar to sequential compositions, hierarchical compositions may form *hierarchical chain*:



(29)

and *hierarchical cycle*:



(30)

(the latter shown with four mappings for graphical convenience, but any plural number of hierarchical compositions may be involved). Hierarchical chains and cycles may be constructed analogously to their algebraic-topological counterparts; the reader is referred to Sections 6.20 and 6.21 of *ML* for details.

Note that, in contrast to a sequential cycle (18), the entailment network of a hierarchical cycle (e.g., diagram (30)) contains two or more *solid-headed arrows*. Efficient causes are relayed, thus a hierarchical cycle is a *closed path of efficient causation*.

8 Clef System and (M,R)-System

The modelling relation (*cf. ML*: Chapter 4) encodes processes in natural systems as mappings in formal systems. This establishes a correspondence between causal entailment in the natural domain and inferential entailment in the formal domain. In particular, efficient causes in natural systems are encoded as efficient causes of mappings.

A hierarchical cycle is, then, the formal-system representation of a closed path of efficient causation in a natural system, so trivially one has the following

Lemma *A natural system has a model containing a hierarchical cycle if and only if it has a closed path of efficient causation.* (*ML*: 6.19)

A natural system is closed to efficient causation if its every efficient cause is entailed within the system (*ML*: 6.23). Thus equivalently,

Theorem *A natural system is closed to efficient causation if and only if it has a model in which all efficient causes are involved in hierarchical cycles.* (*ML*: 6.26)

The equivalence also allows the description *closed to efficient causation* to be used on formal systems, those with *all* efficient causes involved in hierarchical cycles.

Instead of the verbose 'closed-to-efficient-cause system' or 'system that is closed to efficient causation', in Louie and Poli (2011) we have introduced a new term '*clef* system' (for *cl*osed to *ef*ficient causation) with the

Definition A natural system is *clef* if and only if it has a model that has all its processes contained in hierarchical cycles.

The word 'clef' means 'key'; so this terminology has the added bonus of describing the importance of the class of *clef systems*. Analogously, a *clef* formal system is one that has all its mappings contained in hierarchical cycles.

The answer to the "What is life?" question according to the Rashevsky–Rosen school of relational biology is, tersely, that an *organism*—the term is used in the sense of an 'autonomous life form', i.e., any living system (including, in particular, cells)—admits a specific kind of relational description, that it is 'closed to efficient causation'. Explicitly, a material system is an organism if and only if its *every efficient cause is functionally entailed* within the system (*ML*: 11.29). Stated otherwise, an organism is a clef system. This 'self-sufficiency' in efficient causation, closure to functional entailment, is what we implicitly recognize as the one feature that distinguishes a living system from a nonliving one.

In relation to (M,R)-systems (*ML*: Chapters 11 and 12), we may state the Postulate of Life: A natural system is an organism if and only if it realizes an (M,R)-system (*ML*: 11.28). Thus an (M,R)-system is the very model of life; and, conversely, life is the very realization of an (M,R)-system.

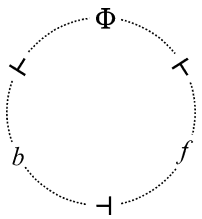
The entailment patterns of the three (M,R)-system maps are

$$\text{metabolism} \quad f \vdash b \tag{31}$$

$$\text{repair} \quad \Phi \vdash f \tag{32}$$

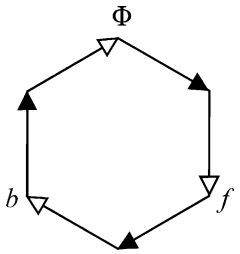
$$\text{replication} \quad b \vdash \Phi \tag{33}$$

whence they functionally entailing one another in cyclic permutation in the entailment diagram:



(34)

The three maps $\{f, \Phi, b\}$ appear in a hierarchical cycle thus:



(35)

One sees that there is cyclic permutational symmetry among the three maps $\{f, \Phi, b\}$: the three functionally entailing processes ⟨metabolism, repair, replication⟩ may be any one of $\langle f, \Phi, b\rangle, \langle \Phi, b, f\rangle$, or $\langle b, f, \Phi\rangle$. Indeed, this 'multitasking' of components has been observed in cells: metabolites may take on epigenetic functions, enzymes may themselves be metabolized, etc.

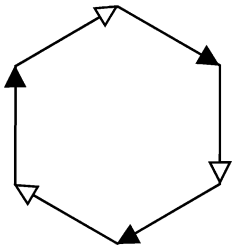
I may also emphasize that an (M,R)-system has as its defining property that of a clef system of mutually functionally entailing mappings. In its simplest form, it is three maps $\{f, \Phi, b\}$ in a hierarchical cycle as in (35), but the maps actually represent *general processes* of a living system, and {metabolism, repair, replication} is only *one possible realization*. Recall (Louie 2006) that these processes describe relational, functional organizations, and there is no one-to-one correspondence between them and the structures that realize them. A functional organization cuts across physical structures, and a physical structure is simultaneously involved in a variety of functional activities. An (M,R)-system is not realized by identifying its objects and mappings in 'concrete' biological components and processes. To tackle the biological realization problem of (M,R)-systems, one ought not to be seeking physicochemical implementations of what the relations *are*, but ought instead to be seeking interpretations of what the relations *do*. The closure in efficient causation of an (M,R)-system is, in short, that of *process* closure. A common interpretative error is the misleading assignment of the label 'catalytic closure' to (M,R)-systems. Even in the canonical {metabolism, repair, replication} realization,

enzymatic catalysis is represented only by *f*, *one* of the three mappings (31)–(33) in the simplest set $\{f, \Phi, b\}$; so the nonsensical label offers an incomplete description at best.

9 Entr'acte: From Symbiosis to Pathophysiology

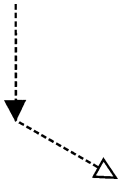
In a previous paper 'Relational biology of symbiosis' (Louie 2010), I formulated relationally the ubiquitous biological interaction of symbiosis. I explicated the topology of the different modes of relational interactions of (M,R)-networks, the entailment diagrams that model the host and the symbiont. These modes all had biological realizations as various categories of symbiotic relationships, ranging from mutualism to parasitism to infection.

The generic hierarchical cycle that is an (M,R)-system distilled into its very essence,



(36)

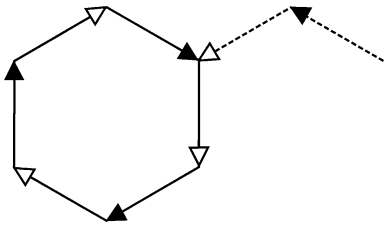
symbolically represents a living system. An additional relational process (e.g., a perturbation of an internal process, an external influence, etc.) is denoted



(37)

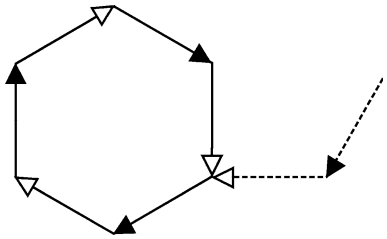
In Louie (2010), diagrams (36) and (37) depicted respectively the host *H* and the symbiont *S* of a symbiotic relationship. The same caveat applies here: the entailment network of an organism is of course a far more complicated relational diagram consisting of a large number of interconnected arrows; but the interactions between these two diagrams are sufficient for my illustrative purposes. I shall continue in what follows to use *H* and *S* when referring to the living system and the additional process, although the two systems may not in general necessarily be in symbiosis (and indeed, *S* may simply be a subsystem of *H*, partitioned for the study of its perturbation effects).

We have learned in Louie (2010) that when the processor of the symbiont supplies its final cause to the host, the effect, realized as *infection*, is often harmful to the latter. In a metabolic interaction, one has



(38)

Most bacterial and fungal infections of organisms are relational biological interactions of this mode. When the symbiont functionally entails a process of the host, as in



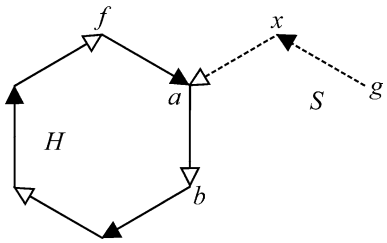
(39)

the infection is often more devastating. This mode of infection, on a higher hierarchical level, is realized variously by infectious agents such as prions and viruses, and some bacteria and fungi.

Pathophysiology is the physiology of abnormality. As a medical subject, it is the study of the changes in biological functions entailed by prodromes, syndromes, or diseases. In terms of relational biology, pathophysiology is, then, the science of decodings and realizations of diagrams (38) and (39). In the rest of this paper I shall elaborate on the interactions in these two relational diagrams, and explore what pathophysiological phenomena, in addition to infection, they may encode and model.

10 Material Entailment as Metabolic Interaction

Let S contain a process g that supplies a new material cause to the metabolic process f of H.



(40)

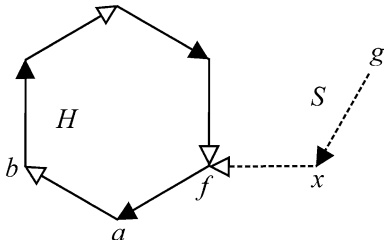
In other words, the material cause a of f is replaced by $a' = g(x)$; in essence, the metabolic process f is replaced by the sequential composite $f \circ g$.
If $f(a') = f(a)$, then the perturbation entailed by g, the variation $f \rightarrow f \circ g$, has no effect. Within the (M,R)-system H, the original entailment $f : a \mapsto b$ becomes $f : a' \mapsto b$; but since the new material cause a' is metabolized by f into the same final cause b, H carries on as before.

If $f(a') \neq f(a)$, however, the original product $b = f(a)$ in the hierarchical cycle of the organism H is then replaced by the different metabolite $b' = f(a')$. The foreign materials a' and b' may be considered infective agents. Most bacterial and fungal infections of organisms are relational biological interactions of this mode, supplying 'foreign materials' into the metabolic network of the host. The immune response and the administration of antibiotics are sample processes that aim to terminate the interaction imposed by S on H. A 'treatment' may proceed in various ways. The most direct process is eliminating g altogether (i.e., the 'termination' of S). It may also work by detaching H and S, thence the two systems are no longer relationally connected (i.e., the 'removal' of S). A third alternative is to modify g sufficiently into g^t (i.e., the 'alteration' of S, by the imposition therein of the functional entailment $\vdash g^t$), so that the new material cause $a'' = g^t(x)$ supplied to f is such that $f(a'') = f(a)$. Then the situation reduces to that in the previous paragraph.

The perturbation $a \rightarrow a'$ of the material input to a metabolic process is not necessarily realized as infection; it may very well be a simple 'change in environment' (e.g., an external stimulus or an internal regulatory trigger). Then the possible reactions of living system H to this perturbation may be interpreted as the *stability* of H with respect to (external- or internal-) environmental change. Indeed, the response of H needs not be reactive, and may be, rather, *anticipatory*. The relational diagram (40) may be reformulated as an anticipatory system (e.g., when various components in H have different internal times scales); but that is the subject for another exposition (*cf. ML*: Chapter 10 and Louie 2012).

11 Functional Entailment of Metabolism

When the substituted node of H is an efficient cause rather than a material cause, the effects are often more consequential. In the interaction

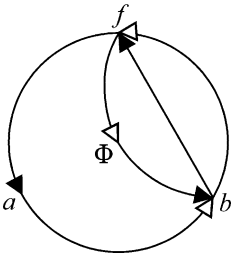


(41)

through the action of the process g, S displaces the original enzyme f in H with an antigen $f' = g(x)$; in essence, the metabolic entailment $f \vdash$ is replaced by the hierarchical composite $g \vdash f' \vdash$.

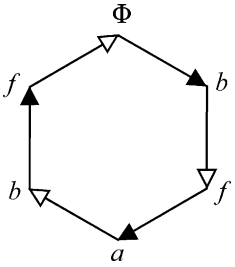
If f' acts the same way as the original $f : a \mapsto b$, then the antigenic effects are limited to that of f' being *itself* a foreign material, whence the situation reduces to that of the previous section on material infection and environmental changes. But if the surrogate enzyme instead catalyses a different metabolic process $f' : a \mapsto b'$ with $b' \neq b$, then the consequences are more serious than the 'new metabolite' case. Since now a new efficient cause f' is in place (and not just a new material cause a' which may be of limited supply), H is infected to *produce* its own infective material. Prions, and some bacteria and fungi, are infectious agents with relational biological interactions of this mode, on a higher hierarchical level.

The perturbation $f \rightarrow f'$ of the efficient cause of a metabolic process is, similar to the material perturbation of the previous section, also not necessarily realized as infection. Metabolic processes may be altered for a variety of reasons, and this is precisely where *repair* enters in. The relational diagram of the simplest (M,R)-system is



(42)

which unfolds into the hierarchical cycle



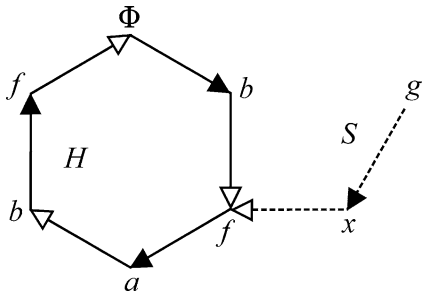
(43)

Note that f has *three* distinct roles in this system:

1. in $f : a \mapsto b$, f is the *efficient* cause;
2. in $\Phi : b \mapsto f$, f is the *final* cause; and
3. in $b : f \mapsto \Phi$, f is the *material* cause.

(A corresponding statement may be made about b, and, indeed, when an isomorphism $a \cong \Phi$ is properly defined, likewise for Φ. This is simply another way of illustrating the cyclic permutational symmetry among the three maps $\{f, \Phi, b\}$.)

With all the nodes of H labelled, interaction (41) appears thus:



(44)

From the entailment paths, one sees that if the original enzyme f in H has been changed (by the process g of S) into f', the repair $\Phi : b \mapsto f$ may be made, hence replenishing the original f.

But note that the material cause (input) of the repair process Φ is b (for this simplest (M,R)-system H—for a general (M,R)-network a repair component receives at least one input from the outputs of the metabolism components of the network, i.e., the final cause of some $\vdash b$ in the network). When

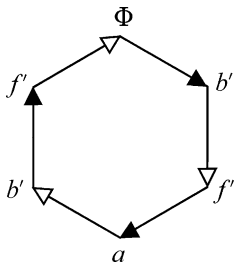
$$g \vdash f' \text{ and } f' \vdash b', \tag{45}$$

the input to Φ may be changed accordingly (depending from which $\vdash b$ the repair process Φ draws its input). In this case, the 'recovery' of f (or the stability of H) depends on what Φ entails from the input b', i.e., on the value of $\Phi(b')$.

Over 50 years ago, Robert Rosen, the creator (or discoverer) of (M,R)-systems, considered the same variational problem (Rosen 1961), albeit from an alterations-in-environment viewpoint rather than my interactions viewpoint. So here is another Rosen-said-it-first disclaimer duly noted. The possible values of $\Phi(b')$ are:

1. $\Phi(b') = f (= \Phi(b))$;
2. $\Phi(b') = f'$;
3. $\Phi(b') = f'' \neq f$ or f'.

In the first case, the perturbation $b \to b'$ does not change the output of Φ, so the metabolism processor f is immediately repaired. In the second case, the replacement metabolic map f' overwhelms the original f, whence the (M.R)-system H changes into H' with a new metabolic form:



(46)

(The reader may have come to the conclusion that in diagram (46), in the entailment of repair Φ, if both perturbations $f \to f'$ and $b \to b'$ take hold, then the replication map could have changed from $b : f \mapsto \Phi$ into $b' : f' \mapsto \Phi'$, entailing a new repair map Φ'. I shall explore this scenario in the next section). In the third case, when yet-another new $\Phi(b') = f''$ is entailed, then the 'stability' of H depends on whether, through iterations of the processes in the (M,R)-network, the sequence of new metabolic maps generated in functional entailment $\vdash f$ is finite or infinite. The metabolic pathways may settle on new stable forms, become periodic, or diverge.

12 Metabolic Entailment of Repair

The change in the metabolic environment $b \to b'$ can result, as we saw in the two previous sections, from two different changes in a metabolic process: the perturbation $a \to a'$ of the material cause or the perturbation $f \to f'$ of the efficient cause. Since the replication map in an (M,R)-system is $b \vdash \Phi$, one may ask whether $b \to b'$ would entail $\Phi \to \Phi'$, i.e., whether metabolic interactions or environmental alterations may produce changes in repair mappings that are the genetic processes. An affirmative will have implications on many biological issues, e.g., the inheritance of acquired characteristics.

To answer this question, I shall need to consider the nature of the replication map $b \vdash \Phi$ in some detail. The 'b' appearing herein is a shorthand, a representation of the general replication map β. A replication map must have as its codomain the hom-set $H(B, H(A, B))$ to which repair mappings Φ belong, whence it must be of the form

$$\beta : Y \to H(B, H(A, B)), \tag{47}$$

with the domain Y a set already existing in the (M,R)-network. Various choices for Y model different modes of entailment of replication in (M,R)-systems (*ML*: Chapter 12).

For the replication map β of the simplest (M,R)-system (which belongs to the first class of entailment of replication), $\beta \cong b$ after the isomorphic identification

$$b \cong \hat{b}^{-1} \tag{48}$$

is made between $b \in B$ and the *inverse evaluation map*

$$\beta = \hat{b}^{-1} \in H(H(A, B), H(B, H(A, B))) \tag{49}$$

(*ML*: 11.16). This mode of replication hinges on the *existence* of the inverse of the evaluation $\hat{b}$ (under a condition that is the algebraic formulation of the *one-gene-one-enzyme hypothesis*). When $b \to b'$, the evaluation map changes correspondingly from $\hat{b}$ to $\hat{b}'$. One readily verifies that *if the inverse* $\hat{b}'^{-1}$ *exists*, then

$$\hat{b}'^{-1}(\Phi(b')) = \Phi, \tag{50}$$

and the repair component Φ is exactly replicated; so the repair map is repaired, and the system 'recovers'. The structures of the hom-sets $H(H(A, B), H(B, H(A, B)))$ determine the existence of inverse mappings. A category-theoretic argument shows

that, for appropriate hom-sets, if $\hat{b}^{-1}$ exists for *some* b, then it exists for *all* b. (The argument is predicate on the hom-sets being 'not too large'. In particular, the hom-sets $H(X, Y)$ in an (M,R)-system must at the very least be a *proper subset* of the set $Y^X = \mathbf{Set}(X, Y)$ of *all* mappings from set X to set Y—evaluation maps in the category **Set** are not *in general* invertible.)

Note that the situation when $b \to b'$, entailing $\Phi(b) \to \Phi(b')$ accordingly, is somewhat different from a *direct* perturbation of $f \to f'$ in $H(A, B)$. While the natural recovery of Φ from $b \to b'$ is an algebraic consequence of the relational organization of an (M,R)-system, additional assumptions are required to make a genetic component Φ invariant to a direct $f \to f'$. This is, however, not to say that mappings somehow have 'memories' of their entailments; it has to do, rather, with the limiting effect of *ranges*. For a mapping to be functionally entailed implies that it must belong to the range of its entailer; this is yet-another illustration of the *proper containment* relation $H(X, Y) \subset \mathbf{Set}(X, Y)$, and containment is by definition restrictive.

In sum, for organisms that are realizations of the (most common) first class of (M,R)-systems, acquired metabolic and physiological changes mostly, under stringent but not prohibitive conditions, do not lead to genetic alterations and are hence not inherited.

13 Alternate Entailments of Replication

While the first class of entailment of replication is 'stable' with respect to metabolic entailment of genetic change, the second class is different. The replication map here is

$$\beta = \gamma_B \in H(B, H(B, H(A, B))) \tag{51}$$

(where γ_B is a Hilbert space conjugate isomorphism; *ML*: 12.7), with a one-to-one correspondence $b \leftrightarrow \Phi$. Indeed, the interaction $\langle b, \Phi \rangle$ may be realized as *enzyme specificity* in enzyme-substrate recognition processes; *ML*: 12.9. (Note, however, that the bijection $b \leftrightarrow \Phi$ is a mathematical result; biology is full of exceptions, and there is evidence that enzyme specificity is not absolute. When it comes to biology, all absolute statements are false, including this one.) Thus a perturbation $b \to b'$ would entail correspondingly $\Phi \to \Phi'$. So in this case, a perturbation of a metabolic component (just as a direct perturbation of the metabolic process $f \to f'$) leads to a change in a genetic process; the effect of S on H, i.e., the new environment or the interaction, is therefore *mutagenic*.

For the third class of entailment of replication,

$$\beta = \pi_S \circ (\,\cdot\,)^{-1} \in H(A, H(B, H(A, B))) \tag{52}$$

(where $\beta : a \mapsto [a^{-1}]_S = \Phi$ is a mapping of similarity classes and models protein biochemistry; *ML*: 12.12). A perturbation $a \to a'$, therefore, may or may not alter the output Φ, depending on whether $[a'^{-1}]_S$ is the same similarity class as $[a^{-1}]_S$. This mode of entailment of replication in (M,R)-systems models alterations in

protein chemistry, and may have epigenetic effects (e.g., nucleic acid methylation and histone acetylation) that affect gene expressions, or may even directly or cumulatively cause mutations.

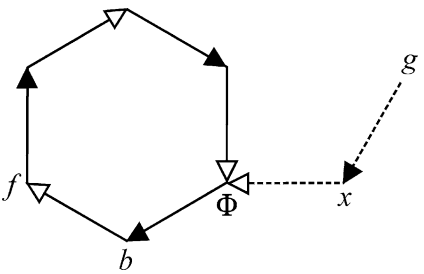
I have deliberately not invoked the term 'Lamarckism' in the foregoing discussion, its use/misuse being a whole separate topic. Let me just say that Jean-Baptiste Lamarck was not a Lamarckian (just as Isaac Newton was not a Newtonian and Charles Darwin was not a Darwinian).

14 Mutagenesis

We have heretofore seen that a metabolic alteration, be it $a \rightarrow a'$, $b \rightarrow b'$, or $f \rightarrow f'$, may or may not engender a genetic change $\Phi \rightarrow \Phi'$ in the (M,R)-system under consideration, the pathophysiological response depending on the topology of the (M,R)-system, on the specific entailment pathways that culminate in $\vdash \Phi$. Both negative and positive responses are, indeed, observed in living systems. Many interactions and environmental changes have harmful but recoverable effects. Others, although not themselves genetic changes, either have epigenetic effects that affect genetic expressions without mutations or indeed be ultimately mutagenic, leading to, for example, cancer and heritable diseases.

The adverb 'ultimately' is important in the previous sentence. This is because mutations may be symptoms and not immediate effects, contrary to what one may often believe. For example, it is an implicit assumption that ionizing radiation *directly* damages the DNA molecule. But perhaps the effect is not so reductionistic molecular: what is damaged by radiation may be a cellular *process*, and DNA *structural* damage was simply a symptom of this *functional* damage, a link further down the causal chain. (Recall that 'function dictates structure' is the *modus operandi* of relational biology, as opposed to the 'structure implies function' of molecular biology). With organisms as realizations of (M,R)-systems, one may readily recognize that what is directly damaged may have been a metabolic process; mutation is manifested when the metabolic perturbation causes a genetic alteration that the replication map β cannot repair.

Some mutagenic environments may, of course, affect cells by *directly* causing mutations. Stated otherwise, the entailment of mutation $\Phi \rightarrow \Phi'$ can also be explicit. Let S contain a process g that affects an internal process f of H on an even higher hierarchical level still, as the genetic interaction



(53)

in which g entails a final cause that replaces the original gene Φ with the rebel $\Phi' = g(x)$. Now the host executes a new genetic instruction $\Phi' : b' \mapsto f'$ instead of the old $\Phi : b \mapsto f$, thus producing new copies of the antigenic enzyme f' for further metabolic devastation. This is how viruses infect, imposing their genes Φ' on the hosts and then subsequently (and hierarchically) using the hosts' metabolic–repair–replication processes to produce more copies of Φ'.

Relational virology will be an upcoming episode in my synthetic continuation in relational biology. Let me simply note in passing here, in a 'teaser' as it were, that one may define 'virus' succinctly as an (M,R)-network that is an 'isolated repair component'! While viruses are not themselves alive, when inside the host cell they *become* alive. In isolation, a virus particle, in relational-biologic terms, consists only of the 'repair' (genetic) component, a very sparse 'non-clef' (M,R)-network. It is only after the initiation of infection, whereupon a virus appropriates the host's 'metabolism' component (indeed all of the host's metabolic–repair–replication processes) for the replication and expression of its viral genome (entailing subsequent release of mature virions from the infected cell), that the virus becomes 'alive', in the sense that its repair component is now part of a clef (M,R)-system. Teleologically, the sole objective of a virus is to replicate the genetic information contained in this repair component, i.e., to express the functional entailment therein.

Just as the perturbations on other hierarchical levels, the mutation $\Phi \rightarrow \Phi'$ is not necessarily realized as a harmful change. What the process g entails may be interpreted as a *gene exchange* between S and H, and may, for example, be a relational model of homologous recombination in meiosis. Indeed, gene exchange is the very definition of *sex* in its most general biological terms. It has been postulated that sex possibly evolved as a mechanism to facilitate the *repair* of damaged genes: in the gene exchange that g functionally entails, H receives an 'intact' gene Φ' from S to replace its own 'broken' gene Φ. In other words, the merits of Φ and Φ' may be reversed, and the new Φ' instituted by the process g of S on H may in fact be *beneficial* to H, either as repair (i.e., the 'R' in (M,R)-systems), or as an inheritable characteristic when manifested improves the competitive fitness of the organism H in its environment.

Mutagenesis is the process of change of the genetic information of an organism, and is the driving force of evolution. We have now learned how mutagenesis may be formulated as entailment in interacting (M,R)-systems. In this light, I invite the reader to review Sections 11B ('The paradoxes of evolution') and 11G ('A word on entailment in evolution') of Robert Rosen's masterwork *Life Itself* (Rosen 1991).

15 Relational Therapeutics

I have explicated earlier how a metabolic perturbation of a living system H by an 'intruder' S (in the most general sense of an extraneous process g of S, external or internal to H) may be remedied: the treatment may be the termination, the removal, or the alteration of S. When g functionally entails a *harmful* process in H, the 'alteration treatment' of modifying g sufficiently into g^t as a countermeasure

becomes relational models of many aspects of *therapeutics*. It is helpful to fix ideas and consider

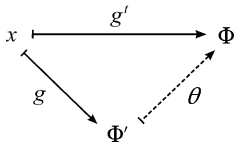
$$g \vdash \Phi', \tag{54}$$

a perturbation of a repair (genetic) map Φ in the (M,R)-system H; but in view of the cyclic permutational symmetry among the three maps $\{f, \Phi, b\}$, Φ may be realized as *any* cellular process, encompassing metabolism, repair, replication, and more. So for generality let $\Phi \in H(Y, Z)$ where Y and Z are appropriate sets (which may themselves be hom-sets) for the role of Φ. (For example, when Φ represents a repair map, it may entail a metabolism map $z \in Z = H(A, B)$ for some sets of metabolites A and B).

Let the domain of g be X; thus $g \in H(X, H(Y, Z))$. If g replaces Φ by $\Phi' = g(x)$ (where $x \in X$), then the ideal therapy $g \to g^t$ would be a treatment process g^t such that $\Phi = g^t(x)$, i.e. the *functional entailment*

$$g^t \vdash \Phi, \tag{55}$$

recovering Φ. The mapping $g^t \in H(X, H(Y, Z))$, however, factors thus



(56)

i.e., into the *sequential composite*

$$g^t = \theta \circ g, \tag{57}$$

where $\theta \in H(H(Y, Z), H(Y, Z))$ with

$$\theta(\Phi') = \Phi. \tag{58}$$

The relation (58) is the conventional wisdom in therapeutics: the symptom Φ' is that which is observed, so it is treated as a material cause in search of a 'reversal therapy' θ that would *materially entail* the normal process Φ. The relational formulation above of the pathophysiological interactions between systems H and S has shown us the therapy that ought to be sought is the *functional entailment* (55) instead.

16 Categorical Therapeutics

The pathogenetic entailment

$$g \in H(X, H(Y, Z)) \tag{59}$$

may be curtailed in an *alternate* therapy if one makes use of the category-theoretic natural isomorphism

$$H(X, H(Y, Z)) \cong H(X \times Y, Z) \tag{60}$$

(cf. relation (28) above). (In what follows let $x \in X$, y, $y' \in Y$, and z, $z' \in Z$).

The effect of the extraneous process g of S on the living system H is the *hierarchical composite* of perturbations

$$\Phi \to \Phi' \text{ and } z \to z', \tag{61}$$

i.e., the mapping

$$g(x) = \Phi' \tag{62}$$

followed by the mapping

$$\Phi'(y') = z'. \tag{63}$$

The remedy

$$g^t \in H(X, H(Y, Z)) \tag{64}$$

is therefore (the search of) a hierarchical composite that would return H from the perturbations (61) to its normal internal processes Φ and z, i.e., ideally the mapping

$$g^t(x) = \Phi \tag{65}$$

followed by the mapping

$$\Phi(y) = z. \tag{66}$$

Because of the isomorphism (60), g^t may equivalently be considered the map

$$g^t(x, y) = z. \tag{67}$$

The therapy (65) followed by (66) is the hierarchical composite entailment

$$g^t \vdash \Phi \vdash z. \tag{68}$$

The isomorphic equivalence (67) is the entailment of the *final* final cause

$$g^t \vdash z. \tag{69}$$

Mathematically, the advantage of (69) over (68) is that, as a problem from which to 'solve' for the 'unknown' g^t, one entailment is simpler than two. (The technical procedures involve 'the inverse function theorem' from functional analysis.) Alternatively, the one equation (67) is easier to solve than the simultaneous equations (65) and (66); in particular, (67) may be solved directly, bypassing the 'intermediate' Φ. Biologically, the search for a process g^t that would entail a specific gene Φ, for the purpose of replacing a mutated gene Φ' in order to restore a specific enzymatic metabolic function $z = \Phi(y)$, is *gene therapy*, the technology of which is still at the beginning of its development. The one-step inversion from the pathological $g(x, y') = z'$ back to $g^t(x, y) = z$, on the other hand, offers an equivalent treatment on the physiological and biochemical level. The two treatments (68) and (69) entail the same end, differing only in their respective efficient causes of achieving it.

The conventional 'reversal therapy' θ in relation (58) may also be helped by the natural isomorphism (60), when one considers

$$\theta \in H(H(Y,Z),\, H(Y,Z)) \cong H(H(Y,Z) \times Y, Z). \tag{70}$$

Thus to solve for the 'unknown' operator θ, instead of working from

$$\theta(\Phi') = \Phi \tag{71}$$

one may use

$$\theta(\Phi', y) = z. \tag{72}$$

The biological advantage of (72) over (71) is as follows. The solution of (72) for θ is the entailment

$$\{\Phi', y, z\} \vdash \theta, \tag{73}$$

where the pathological condition Φ' is observable and the causes y and z are on lower hierarchical levels (e.g., when Φ' is a defective gene, y is a metabolite and z is an enzyme). On the other hand, the solution of (71) for θ is the entailment

$$\{\Phi', \Phi\} \vdash \theta, \tag{74}$$

which requires the a priori knowledge of the normal process Φ in addition to the observed Φ'.

17 Pathogenetic Strategies and Carcinogenesis

One may speculate that the pathogenetic entailment

$$g(x) = \Phi' \tag{75}$$

with

$$g \in H(X, H(Y, H(A, B))) \tag{76}$$

may also proceed through the mapping's isomorphically equivalent form

$$g \in H(X \times Y, H(A, B)). \tag{77}$$

So the infection g, instead of entailing as the mapping (76) a *direct* mutation $\Phi \to \Phi'$, may equivalently entail as the mapping (77) with its *primary* final cause the epigenetic perturbation $f \to f'$, in the form of

$$g(x, y) = f'. \tag{78}$$

(The discussion in Sect. 12 above on range restriction similarly applies here: a perturbation $f \to f'$ entailed by (78) is not arbitrary, it being limited by the range of the entailer g, i.e., limited by the structure of the hom-set $H(X \times Y, H(A, B))$. So the infection strategy (78) is still on the hierarchical level of $\Phi \to \Phi'$; it is simply, through the isomorphic equivalence $H(X, H(Y, H(A, B))) \cong H(X \times Y, H(A, B))$, *implementing its efficient cause* on a lower level).

The *primary* epigenetic perturbation $f \to f'$ entailed by g then causes the *secondary* metabolic change $b \to b'$, which in turn achieves the *tertiary* final cause $b' \vdash \Phi'$. Stated otherwise, as the mapping (77), g institutes the causal chain

$$f \to f',\ b \to b',\ b' \vdash \Phi', \tag{79}$$

traversing the hierarchical cycle of H to arrive at the same effect Φ'. The biological advantage (for the invader) of the multistep pathogenetic strategy (79) over the direct $g \vdash \Phi'$ as the mapping (76) is that an organism is often more vigilant on its defence on the genetic level against direct mutagenesis $\Phi \to \Phi'$. (Trivially, for the example of a eukaryotic cell, there is at least the additional physical barrier of the nuclear membrane to breach). But the strategy (79) 'stealthily' infects on the enzymatic level, and then 'hijacks' the organism's metabolism–repair–replication processes to cause the functional entailment $\vdash \Phi'$ from within.

The astute reader will have noticed that the hom-set $H(X \times Y, H(A, B))$ in (77) is such that its mappings have the hom-set $H(A,\ B)$ as their codomin. So the isomorphic equivalence (60) may be iterated, and one has a third description of the entailer

$$g \in H(X \times Y \times A, B), \tag{80}$$

with

$$g(x, y, a) = b'. \tag{81}$$

With g in this form, the primary infection strategy is the metabolic change $b \to b'$, which in turn entails the final $b' \vdash \Phi'$. (As similarly noted above, the change $b \to b'$ is not arbitrary in B: the representation (80) implicitly restricts the range of g to a proper subset of its codomain; i.e.,

$$g(X \times Y \times A) \subset B \tag{82}$$

is proper containment). In this infection strategy, the 'stealth' is two hierarchical levels down from the final mutagenesis $\Phi \to \Phi'$.

It has not escaped my notice that the category-theoretic alternate therapy I have postulated immediately suggests a possible course of treatment of the *organizational disease* that is cancer, for which the relational interactions that I have been exploring may be considered the invasion of a living system H by a carcinogenic S. A scenario similar to the iterative generation of new metabolic maps in functional entailment $\vdash f$ (as I have explained in Sect. 11 above) can also happen here with $\vdash \Phi$. While the behaviour of the sequence

$$f \to f' \to f'' \to f''' \to \cdots \tag{83}$$

is realized in terms of the stability of H in response to metabolic perturbations, here repeated 'exposure' to the process g of S may engender *multistep* genetic changes

$$\Phi \to \Phi' \to \Phi'' \to \Phi''' \to \cdots, \tag{84}$$

each step reflecting a genetic change that *cumulatively* transforms a normal cell into a malignant cell. Further details of this *relational oncology* will be forthcoming.

18 Postludium

Disease may be defined as any condition that impairs normal function of an organism. It may be classified into two broad categories, internal dysfunction and external perturbation. An internal dysfunction may, for example, be some control error with the homeostatic mechanism, or some sort of defect in the inherent organization of the organism itself. An external perturbation occurs when one organism interacts with another, or simply when an organism encounters an inhospitable environment. We have seen that both classes of diseases may readily be studied relationally, through interactions between a living system H and an errant process S.

In this paper we have learned how one can study the various ways in which the metabolism–repair–replication processes in a living system can get interrupted—metabolic perturbation, genetic perturbation, epigenetic perturbation, or some combination thereof. The entailed pathophysiology is to see what the consequences would be, and to see whether or not the effects are therapeutically reversible. We have discovered how relational biology may provide important insights into the kinds of causes of such physiological interruptions, and the kinds of medical ways available for undoing them. When there is cause there is often a 'counter-cause' that can be identified, but it may be on a different hierarchical level, the remedy appearing elsewhere in the causal chain. Also, the category theory of functional entailment has shown us that both pathogenesis and therapeutics may be manifested in naturally isomorphic equivalent forms, with different degrees of subtlety in their realizations.

Robert Rosen arranged the relational organization in his (M,R)-systems in such a way that repair is a mapping that produces a mapping as output: for the 'R' part, instead of just producing something to be operated on, it could produce an operator. Rosen considered this, the entailment of a mapping, his deepest insight: the innovation is the biological realization of functional entailment

$$\vdash f, \tag{85}$$

the fact that processes themselves may be treated like any other material. A happy happenstance was the connection of this relational theory of biological systems to category theory (the two theories born within a decade of each other in the middle of the Twentieth century), when Rosen found himself equipped with a ready-made mathematical tool. While it may not always be immediately apparent, it may be said that almost all of Rosen's scientific works are consequences from a consideration of problems arising in the study of (M,R)-systems. Every time one looks at (M,R)-systems they have something new to offer.

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