

## **A Phenomenological Calculus for Recognition Processes**

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Using enzyme–substrate recognition as an example, a phenomenological calculus for recognition processes is developed. Recognition is derived as one aspect of a general phenomenology of the causal relationship. Rather than considered as an isolated process, recognition is thus analyzed in its functional context as a characteristic feature of a system which responds to specific inputs to produce specific outputs. The mathematical formulation of the concept of system response and the associated description of a system in terms of response lead directly to a metric calculus providing a quantitative measure for discrimination. Moreover, the metric structure inherent in this phenomenology allows one to determine the functional relationship between the physical features used by the system to recognize an input (e.g. a substrate) and corresponding features possessed by the output (e.g. the product). The phenomenological calculus is derived from a set of elementary postulates.

The system is divided into distinct, interacting subsystems, indexed by a finite set  $\{i = 1, 2, \dots, m\}$ . The set of causes imposed upon the system (i.e. the input) is given by various  $F_i$  belonging to some Hilbert space  $H$ . The system is characterized by a fixed set of constitutive parameters,  $a^i$ , which belong to the dual space  $H^*$ . The system dynamics is phenomenologically described by a “response” tensor given by the dyadic  $\mathbf{R} = a^i F_i$ . It is postulated that  $\mathbf{R}$  is invariant with respect to transformations of the representation, that is, with respect to a change of constitutive parameters. In particular,  $\mathbf{R}$  has an invariant dual representation.

In the example of enzyme–substrate recognition, the  $a^i$ 's represent enzymes and the  $F_i$ 's represent substrates. The recognition process is given by the evaluation  $a^i(F_i)$ , while the enzyme–substrate complex is represented by the response tensor  $a^i F_i$ . The dual representation is the mathematical analogue of the enzyme–product complex. The paper closes with the analysis of membrane transport and dissipative systems, from which the idea of the response tensor originated.

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## 1. Introduction

Recognition and its correlate, discrimination, are, in the true sense of the word, vital. Recognition is the foundation of the extreme specificity of biological processes and is the basis of control. Nearly every biological process provides an example: the immune response discriminates between self and not-self. Enzymes are justly famous for their precision in the recognition of specific substrates. In excitable membranes, electrical activity is governed by variations in the membrane's ability to discriminate between various ions. It is impossible to conceive of the regulation of metabolism without the recognition processes expressed in passive permselectivity or in carrier-mediated transport. At every step in the synthesis of proteins under the control of information-bearing macromolecules there is a recognition process.

Recognition processes will be the central concern of this paper but the goal of the analysis will be far more than just a model for recognition processes, *per se*. That is, recognition will not be considered as an isolated, primary phenomenon, to be analysed separate from the more comprehensive functional context in which recognition processes occur. In their seminal paper on enzyme-substrate recognition, Edelstein & Rosen (1978) point out that any given recognition process "triggers programmed responses . . . or to be more precise, it sets the initial conditions for a complicated dynamic process which follows it." As it was, however, they attacked the problem of recognition directly, outside the context of the dynamics in which it is embedded—the transformation of substrate to product. Nevertheless, their mathematical model for enzyme-substrate recognition can be extended in a simple and natural way to include a quantitative measure of the relationship between the structural features of the substrate and those of the product. This will be one result of the phenomenology we will develop to represent dynamical systems based upon the recognition process.

Our approach to the problem of recognition starts with the construction of a phenomenological description of the general dynamical situation wherein the system acts as mediator between "causes" presented and specific "effects" produced. This phenomenological calculus is based upon a simple function which serves as a measure of the "response" of the system to the given cause presented to (or imposed upon) it. Implicit in the idea of response is the germ of recognition, and the quantification of recognition is a direct consequence of the metrical structure inherent in this phenomenological calculus.

This phenomenology was originally developed in a context which seemed strictly dynamical, namely, the elucidation of the structure of irreversible

thermodynamics: Richardson† (1980). In a sequel, Richardson, Louie & Swaminathan† (1982), it was demonstrated that all the linear phenomenology of irreversible thermodynamics could be derived from three simple postulates on the nature of the representations used to describe the response of a system to imposed forces (or to causes presented). In this second paper, the mathematical characterization of response was extended beyond the limited context of irreversible thermodynamics and applied to the problem of biological aging.

The phenomenological calculus presented in R-L-S-82 can be applied to a large class of dynamical systems, being general in derivation and not at all restricted to the two examples considered. However, it is restricted in a mathematical sense in that the imposed forces (i.e. generalized causes) must be represented as finite-dimensional vectors. In a practical sense, this is no great restriction because there is no restriction on how finite—one could propose a force (cause) vector of dimension  $n = 1000$ . Nevertheless, there is a great difference between the practical and theoretical. By developing in this paper a phenomenological calculus which is based upon infinite-dimensional vector spaces, we shall discover a tool of remarkable generality, particularly well-suited to study systems when the recognition process underlies the dynamics. The Edelstein & Rosen (1978) enzyme–substrate recognition scheme is shown to be a subclass of this phenomenology.

## 2. The Response Tensor and Description Space

In a practical and very successful manner, phenomenology has long been used in the biological sciences. A set of causes,  $\{C_i\}$ , is directly related to the set of observed effects,  $\{E^i\}$ , by means of curve fitting. Compartment analysis provides an example of the phenomenological reduction of kinetic data, while the Hodgkin–Huxley equations are a famous example of a phenomenological description of an electro-physiological process by curve fitting. Such direct phenomenological models can be represented by scheme (a) in Fig. 1. The system upon which the causes act is not explicitly evident, and it is only *a posteriori* that the parameters of the curve-fit are given interpretation in the context of the system.

In the phenomenological calculus developed in R-80 and R-L-S-82, the system enters in a direct and primary manner. The relationship between cause and effect is secondary to, and derived from, the response of the system to the causes imposed. As it will be used later in a discussion on recognition processes, let us review the basic tenets of the above-mentioned papers in the notation of irreversible thermodynamics. The causes,  $C_i$ , are

† Hereafter referred to as R-80 and R-L-S-82.

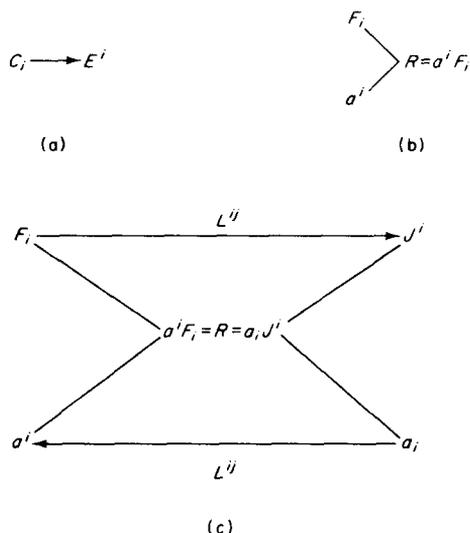


FIGURE 1.

the forces per mole of species  $i$ :  $C_i \equiv F_i$ . The effects,  $E^i$ , are just the molecular fluxes produced by these imposed forces:  $E^i \equiv J^i$ . There are three postulates.

*Postulate 1.* The specification of the forces,  $\{F_i\}$ , acting upon a system and the set of the constitutive parameters,  $\{a^i\}$ , conjugate to those forces is sufficient to determine a phenomenological description of the system dynamics.

*Postulate 2.* The system dynamics is characterized phenomenologically by a dyadic called the response tensor,  $\mathbf{R} \equiv a^i F_i$ .

*Definition.* The space spanned by  $\mathbf{R}$  is called description space.

*Postulate 3.* The response tensor is invariant under co-ordinate transformations in description space.

Postulates 1 and 2 are indicated by scheme (b) in Fig. 1. Postulate 3 implies that there are other representations of the response tensor. In particular, one may write  $\mathbf{R}$  in terms of the components  $\{J^i\}$  dual to the components  $\{F_i\}$ . This representation is indicated by the right hand side of scheme (c) in Fig. 1. Postulate 3 states that the response tensor  $\mathbf{R}$  given in terms of a system dynamics described in terms of causes  $\{F_i\}$  is the same as that described in terms of effect  $\{J^i\}$ .

By definition, the components dual to  $\{\mathbf{F}_i\}$  are given by the projection of  $\mathbf{R}$  upon the co-ordinate vector  $\mathbf{a}^i$ . That is

$$\begin{aligned} \mathbf{J}^i &\equiv \mathbf{a}^i \cdot \mathbf{R} \\ &= (\mathbf{a}^i \cdot \mathbf{a}^j) \mathbf{F}_j \\ &= L^{ij} \mathbf{F}_j. \end{aligned} \tag{1}$$

Thus cause and effect (i.e.  $\mathbf{F}_j$  and  $\mathbf{J}^i$ ) are phenomenologically related by a metric tensor having elements  $L^{ij} \equiv \mathbf{a}^i \cdot \mathbf{a}^j$ . In R-L-S-82 it was shown that the response tensor  $\mathbf{R}$  forms a metric space, with the norm  $|\mathbf{R}|^2 = \mathbf{R} : \mathbf{R} = L^{ij} \mathbf{F}_i \cdot \mathbf{F}_j \geq 0$ . Thus, from these three postulates based upon the concept of system response one arrives at a phenomenological calculus with an inherent metrical structure.

### 3. Hilbert Space and its Dual

We shall now proceed to extend the mathematical formalism. Instead of letting the domain of the causes be the finite-dimensional inner product space  $\mathbb{R}^n$  (as in R-L-S-82), we shall consider a general (possibly infinite-dimensional) Hilbert space.

Throughout this paper,  $H$  will denote a real Hilbert space with inner product  $\langle \cdot, \cdot \rangle$  and norm  $\|\cdot\|$  (related of course by  $\|x\| = \langle x, x \rangle^{1/2}$ ). Of particular interest to us will be the Euclidean space  $H = \mathbb{R}^n$  with  $\langle x, y \rangle = x \cdot y$  and the Hilbert space  $H = L^2(\mu)$  of all square-integrable real-valued functions on a measure space  $(X, M, \mu)$  with  $\langle x, y \rangle = \int_X xy \, d\mu$ .

It is well-known that  $a$  is a bounded linear functional on  $H$  (i.e.  $a \in H^*$ ) if and only if there exists a unique  $y \in H$ ,  $a(x) = \langle x, y \rangle$ . Further,  $\|a\|^* = \|y\|$  where  $\|\cdot\|^*$  denotes the operator norm of  $a$ ,

$$\|a\|^* = \sup \{ \|a(x)\| : \|x\| = 1 \}. \tag{2}$$

(This is one of the many so-called Riesz representation theorems in functional analysis.) Thus, there is a one-to-one mapping  $\Phi$  of  $H^*$  onto  $H$  which satisfies

$$a(x) = \langle x, \Phi a \rangle \tag{3}$$

for all  $x \in H$  and all  $a \in H^*$ . It is easy to see that

$$\Phi(a + b) = \Phi(a) + \Phi(b) \quad \text{and} \quad \Phi(ra) = r\Phi(a) \tag{4}$$

for all  $a, b \in H$  and all  $r \in \mathbb{R}$ . So  $\Phi$  is a linear mapping. Also,

$$\|\Phi a - \Phi b\| = \|\Phi(a - b)\| = \|a - b\|^*. \tag{5}$$

So  $\Phi$  is a linear isometry of  $H^*$  onto  $H$ . By defining

$$\langle a, b \rangle^* = \langle \Phi a, \Phi b \rangle, \quad (6)$$

we see that  $\langle \cdot, \cdot \rangle^*$  is an inner product on  $H^*$  and

$$\|a\|^* = (\langle a, a \rangle^*)^{1/2}. \quad (7)$$

So in fact  $\Phi$  is a Hilbert space isomorphism from  $H^*$  to  $H$  and  $H^*$  is a real Hilbert space with inner product  $\langle \cdot, \cdot \rangle^*$  and norm  $\|\cdot\|^*$ . In other words,  $H$  can be considered as “self-dual” and in fact quite often the identification  $H^* = H$  is made. But we shall distinguish between members of  $H$  (“contravariant vectors”) and members of  $H^*$  (“covariant vectors”) to keep the ideas straight.

#### 4. Products of Hilbert Spaces

Let  $(H_i, \langle \cdot, \cdot \rangle_i, \|\cdot\|_i)$ ,  $i = 1, 2$ , be two real Hilbert spaces. On the product space  $H_1 \times H_2$  we can define a function

$$\langle \cdot, \cdot \rangle: (H_1 \times H_2) \times (H_1 \times H_2) \rightarrow \mathbb{R} \quad (8)$$

by

$$\langle (x_1, x_2), (y_1, y_2) \rangle = \langle x_1, y_1 \rangle_1 + \langle x_2, y_2 \rangle_2. \quad (9)$$

It is easy to check that  $\langle \cdot, \cdot \rangle$  is an inner product on  $H_1 \times H_2$  and that the metric induced by the corresponding norm  $\|\cdot\|$  is complete. So  $(H_1 \times H_2, \langle \cdot, \cdot \rangle, \|\cdot\|)$  is a Hilbert space. The norm topology of  $H_1 \times H_2$  induced by  $\|\cdot\|$  is in fact the product topology of the respective norm topologies on  $H_1$  and  $H_2$ .

It is clear that this construction of product Hilbert spaces can be extended to any finite product. We shall only be concerned with the product space  $H^* \times H$ . The inner product on  $H^* \times H$  is defined by

$$\begin{aligned} \langle (a, x), (b, y) \rangle &= \langle a, b \rangle^* + \langle x, y \rangle \\ &= \langle \Phi a, \Phi b \rangle + \langle x, y \rangle \end{aligned} \quad (10)$$

with associated norm

$$\begin{aligned} \|(a, x)\| &= [(\|a\|^*)^2 + \|x\|^2]^{1/2} \\ &= [\|\Phi a\|^2 + \|x\|^2]^{1/2} \end{aligned} \quad (11)$$

#### 5. The Space $T_1^1(H)$

Let  $y \in H$  and  $b \in H^*$ . Let  $y \otimes b$ , called the *tensor product* of  $y$  and  $b$ , be defined as the bilinear mapping from  $H^* \times H$  to  $\mathbb{R}$  whose action on

$(a, x) \in H^* \times H$  is

$$(y \otimes b)(a, x) = a(y)b(x) = \langle y, \Phi a \rangle \langle x, \Phi b \rangle. \quad (12)$$

In the language of tensor theory, a bilinear mapping from  $H^* \times H$  to  $\mathbb{R}$  is called a *tensor of type (1,1) over  $H$* . The collection of all tensors of type (1,1) over  $H$  is denoted by  $T_1^1(H)$ . A typical member of  $T_1^1(H)$  is a finite sum of tensors of the form  $y_i \otimes b^i$  where  $y_i \in H$  and  $b^i \in H^*$ , and we shall denote it simply by  $y_i \otimes b^i$  using Einstein's summation notation ( $= \sum_{i=1}^m y_i \otimes b^i$ ). Its action on  $(a, x) \in H^* \times H$  is defined naturally by

$$(y_i \otimes b^i)(a, x) = \langle y_i, \Phi a \rangle \langle x, \Phi b^i \rangle. \quad (13)$$

### 6. Dyads and Dyadics over $H$

Let  $y \in H$  and  $b \in H^*$ . We define the *dyad* to be

$$by = \Phi b \otimes \Phi^{-1} y. \quad (14)$$

In other words, the dyad is a bilinear mapping from  $H^* \times H$  to  $\mathbb{R}$  ( $by \in T_1^1(H)$ ) sending  $(a, x)$  to

$$\begin{aligned} by(a, x) &= (\Phi b \otimes \Phi^{-1} y)(a, x) \\ &= \langle \Phi b, \Phi a \rangle \langle x, y \rangle \\ &= \langle a, b \rangle^* \langle x, y \rangle. \end{aligned} \quad (15)$$

A finite linear combination of dyads is called a *dyadic*.

Since  $\Phi: H^* \rightarrow H$  is in particular a bijection, the tensors  $\Phi b^i \otimes \Phi^{-1} y_i$ , as  $b^i$  and  $y_i$  range over all finite collections in  $H^*$  and  $H$ , respectively, span the whole of  $T_1^1(H)$ . Thus the collection of all dyadics is the whole space  $T_1^1(H)$ ; i.e. every tensor of type (1,1) over  $H$  has a representation as a dyadic via

$$x^i \otimes a_i = (\Phi^{-1} x^i)(\Phi a_i). \quad (16)$$

### 7. The Double Inner Product

For  $a^i x_i$  (sum over  $i = 1, 2, \dots, m$ ) and  $b^j y_j$  (sum over  $j = 1, 2, \dots, n$ ) in  $T_1^1(H)$ , we define their *double inner product* to be the real number

$$\begin{aligned} \langle\langle a^i x_i, b^j y_j \rangle\rangle &= \langle a^i, b^j \rangle^* \langle x_i, y_j \rangle \quad (\text{sum over } i \text{ and } j) \\ &= \langle \Phi a^i, \Phi b^j \rangle \langle x_i, y_j \rangle. \end{aligned} \quad (17)$$

One can easily check that the definition is independent of the representation

of the dyadics—i.e. if  $a^i x_i = a^{i'} x_{i'}$  and  $b^j y_j = b^{j'} y_{j'}$ , then

$$\langle\langle a^i x_i, b^j y_j \rangle\rangle = \langle\langle a^{i'} x_{i'}, b^{j'} y_{j'} \rangle\rangle \quad (18)$$

and that  $\langle\langle \cdot, \cdot \rangle\rangle$  is an inner product on  $T_1^1(H)$ . However,  $T_1^1(H)$  is not necessarily complete with respect to the norm associated with  $\langle\langle \cdot, \cdot \rangle\rangle$ , thus  $T_1^1(H)$  itself may not be a Hilbert space.

### 8. Description Space

Let  $a^1, a^2, \dots, a^m$  be fixed in  $H^*$ . Let  $D = \{a^i x_i \text{ (sum over } i): x_1, x_2, \dots, x_m \in H\}$  be called the *description space* determined by  $\{a^1, \dots, a^m\}$ . It is clear that  $D$  is a linear subspace of  $T_1^1(H)$  and so  $(D, \langle\langle \cdot, \cdot \rangle\rangle)$  is an inner product space. For  $i, j = 1, 2, \dots, m$ , let the *phenomenological coefficients* be

$$L^{ij} = \langle a^i, a^j \rangle^* = \langle \Phi a^i, \Phi a^j \rangle. \quad (19)$$

Then for  $a^i x_i, a^j y_j \in D$ ,

$$\langle\langle a^i x_i, a^j y_j \rangle\rangle = L^{ij} \langle x_i, y_j \rangle. \quad (20)$$

Let  $\|\cdot\|$  be the norm on  $D$  associated with  $\langle\langle \cdot, \cdot \rangle\rangle$ ; then

$$\|a^i x_i\|^2 = L^{ii} \langle x_i, x_i \rangle \geq 0. \quad (21)$$

One easily sees that for each  $k = 1, 2, \dots, m$

$$\begin{aligned} 0 &\leq L^{kk} \|x_k - y_k\|^2 \text{ (no sum)} \leq \|a^i x_i - a^i y_i\|^2 \\ &\leq |L^{ij}| \|x_i - y_i\| \|x_j - y_j\| \end{aligned} \quad (22)$$

holds. Hence a sequence  $\{a^i x_{\alpha,i}\}_\alpha$  converges to  $a^i x_i$  in  $D$  if and only if, for each  $i$ , the sequence  $\{x_{\alpha,i}\}_\alpha$  converges to  $x_i$  in  $H$ . Since  $H$  is complete, this implies that  $D$  is also complete, whence  $(D, \langle\langle \cdot, \cdot \rangle\rangle, \|\cdot\|)$  is a Hilbert space. Note that although  $T_1^1(H)$  may not be complete,  $D$ , which is essentially a “finite dimensional subspace” of  $T_1^1(H)$ , is complete.

### 9. Postulates

Let us now make explicit the basic axioms in our analysis of complex system dynamics. We are essentially rephrasing the three postulates in section 2 in our Hilbert space context.

*Postulate 1.* A complex system is divided into distinct, interacting subsystems, indexed by a finite set  $\{i = 1, 2, \dots, m\}$ . The system is characterized

by a fixed set of constitutive parameters  $\{a^i \in H^*: i = 1, 2, \dots, m\}$ . The set of causes imposed on the system is described by various  $F_1, F_2, \dots, F_m \in H$ .

*Postulate 2.* The system dynamics corresponding to the sets of causes  $\{F_i\}$  are characterized phenomenologically by the dyadic response tensor  $\mathbf{R} = a^i F_i$ .

*Postulate 3.* The space spanned by  $\mathbf{R}$  is the description space  $D = \{\mathbf{R} = a^i F_i : F_1, F_2, \dots, F_m \in H\}$  and  $\mathbf{R}$  is invariant with respect to representations (i.e. alternate descriptions of the dynamics) as a member of  $T_1^1(H)$ .

### 10. Dual Representation

Proceeding analogously as in R-L-S-82, let us now define the *effects* in  $D$  corresponding to a set of causes  $\{F_i\}$  to be, for  $j = 1, 2, \dots, m$ ,

$$J^j = \mathbf{R}(a^j, \cdot) = \langle a^j, a^i \rangle * F_i \in H^*, \tag{23}$$

that is,

$$J^j = L^{ij} F_i \tag{24}$$

Suppose now we want to find  $a_1, a_2, \dots, a_m \in H$  such that we can write  $\mathbf{R}$  in a dual representation

$$\mathbf{R} = a^i F_i = a_j J^j \tag{25}$$

Then we have

$$a^i F_i = a_j J^j = a_j L^{ij} F_i \tag{26}$$

whence for all choices of  $F_i, \dots, F_m$  in  $H$

$$(a^i - a_j L^{ij}) F_i = \mathbf{0}. \tag{27}$$

Thus

$$a^i - a_j L^{ij} = 0 \in H^* \tag{28}$$

that is,

$$L^{ij} a_j = a^i. \tag{29}$$

(The transition from equation (28) to equation (29) uses the fact that the  $m \times m$  real matrix  $(L^{ij})$  is symmetric.)

The set  $\{a_j\}$  would be determined uniquely if the Gram matrix  $(L^{ij})$  of  $\{a^i\}$  were invertible. But this in general is not the case and we have some degrees of freedom in picking the solution  $\{a_j\}$  to equation (29). This has

interesting interpretations in the context of the unidirectionality of causes and effects, and the reader is referred to R-L-S-82 for details. The dual representation of  $\mathbf{R}$  is depicted in Fig. 1(c).

### 11. $H = L^2(\mu)$

The treatment of the special case when  $H$  is the Euclidean space  $\mathbb{R}^n$  with  $\langle x, y \rangle = x \cdot y$  is the content of R-L-S-82, to which the reader again is referred for details.

Let us look at another special case when  $H = L^2(\mu)$ , the space of all square-integrable real-valued functions on a measure space  $(X, M, \mu)$ . Note this is in fact the general case because it is known that every non-trivial Hilbert space is isomorphic to  $l^2(A)$  for some set  $A$  (via Fourier series representations). But we shall not dwell on this point here.

In  $L^2(\mu)$ ,

$$\langle x, y \rangle = \int_X xy \, d\mu. \tag{30}$$

The statement of the Riesz Representation Theorem is

$$a(x) = \langle x, \Phi a \rangle = \int_X x \Phi a \, d\mu \tag{31}$$

and instead of considering  $L^2(\mu)^* = L^2(\mu)$  via  $a \mapsto \Phi a$  we could use the identification  $a \mapsto \Phi a \, d\mu$  which sends  $L^2(\mu)^*$  into the space  $M(\mu)$  of all measures which are absolutely continuous with respect to  $\mu$ . So we can consider  $L^2(\mu)^* \rightarrow M(\mu)$  as well.

The double inner product on  $T_1^1(L^2(\mu))$  is

$$\langle\langle a^i x_i, b^j y_j \rangle\rangle = \left( \int_X \Phi a^i \Phi b^j \, d\mu \right) \left( \int_X x_i y_j \, d\mu \right). \tag{32}$$

Fixing  $a^1, a^2, \dots, a^m \in L^2(\mu)^*$  and letting the description space be  $D = \{a^i F_i : F_1, F_2, \dots, F_m \in L^2(\mu)\}$ , we have

$$\langle\langle a^i F_i, a^j G_j \rangle\rangle = L^{ij} \int_X F_i G_j \, d\mu. \tag{33}$$

The effects in  $D$  corresponding to  $\{F_i\}$  are

$$J^j = L^{ij} F_i = L^{ij} \int_X F_i \, d\mu \in L^2(\mu)^*. \tag{34}$$

Thus  $J^j$  can be considered as the measure  $L^{ij} F_i \, d\mu \in M(\mu)$ .

**12. An Application: Enzyme-Substrate Recognition**

A model for enzyme-substrate recognition is presented in Edelman & Rosen (1978). The theory rests on the following two assumptions.

- (1) That substrates can be represented by continuous functions, which vanish outside some closed bounded region in  $\mathbb{R}^3$ , analogous to charge or mass distributions; i.e. substrates are represented by elements  $F \in C(K)$ , the space of all real-valued continuous functions on  $K$ , where  $K$  is a compact subset of  $\mathbb{R}^3$  chosen to be large with respect to molecular dimensions.
- (2) That recognition of the substrate corresponds to the evaluation of a linear functional on  $C(K)$ —or what is equivalent:
- (2') That associated with a given enzyme is a function  $a$  in the dual space of  $C(K)$ , i.e.  $a \in NBV(K)$ , the space of all real-valued, normalized functions on  $K$  of bounded variation, and that recognition of a substrate  $F$  results from the evaluation of Stieltjes integral of one form  $\int F da$ .

(The equivalence of (2) and (2') is due to yet another theorem known as the Riesz Representation Theorem.)

These assumptions are summarized in Fig. 2.

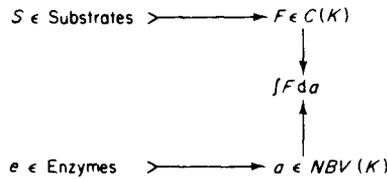


FIGURE 2.

Note that the continuous function  $F$  representing an enzyme portrays the “shape” of the molecule and describes the location and orientation of the substrate relative to the active site—these are the factors which play an important role in the recognition process. Thus the recognition problem as analysed here is based on the structural relationships between the substrate and the product and not on the dynamics of the transformation. The reader is referred to Edelman & Rosen (1978) for details.

How can we formulate this model in terms of our Hilbert description spaces? Consider the measure space  $(K, M, m)$  where  $M$  is the  $\sigma$ -algebra of all Lebesgue measurable subsets of  $K$  and  $m$  is the Lebesgue measure on  $M$ , and consider the Hilbert space  $L^2(m)$ . Now  $C(K)$ , equipped with the supremum ( $L^\infty$ ) norm, is a closed linear subspace of  $L^\infty(m)$  (hence

complete). Since  $m(K) < \infty$ , for  $0 < r < s \leq \infty$   $\|x\|_r \leq \|x\|_s$ , whence  $L^r(m) \supset L^s(m)$ . So in particular  $L^\infty(m) \subset L^2(m) \subset L^1(m)$ , and we have the situation depicted in Fig. 3.

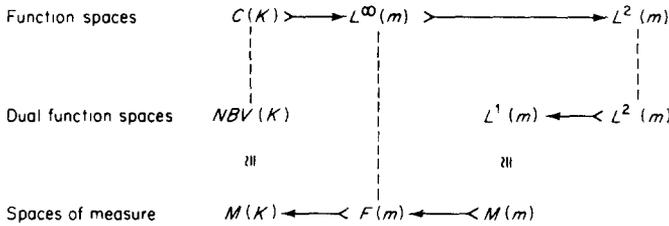


FIGURE 3.

The Banach space isomorphism  $NBV(K) \cong M(K)$  is due to a theorem on the differentiation of measures (Rudin, 1974, Theorem 8.14), where  $M(K)$  is the space of all bounded, signed, regular measures on  $K$ .  $F(m)$ , the space of all bounded, signed, finitely additive measures on  $K$  which are absolutely continuous with respect to  $m$ , is the dual space of  $L^\infty(m)$  (Hewitt & Stromberg, 1975, Theorem 20.35). The fact that  $L^1(m)$  and  $M(m)$  are isomorphic as Banach spaces is the statement of the Radon-Nikodym theorem (Hewitt & Stromberg, 1975, Theorem 19.23), the correspondence being  $h \leftrightarrow \mu$  via  $h \, dm = d\mu$ , and  $h = d\mu/dm$  is known as the Radon-Nikodym derivative of  $\mu$  with respect to  $m$ .

With this framework, we can extend the space  $C(K)$  to  $L^2(m)$  and the situation in Fig. 2 can then be generalized to that in Fig. 4. While the

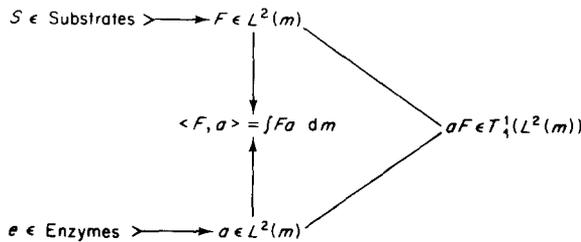


FIGURE 4.

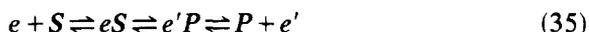
evaluation of the linear functional  $a$  at  $F$  represents enzyme-substrate recognition, the dyad  $aF$  can be interpreted as the enzyme-substrate complex, the intermediate species in their interactions.

There is no need to repeat or elaborate the lucid and thorough discussion of Edelman & Rosen (1978) on the biological implications of this theory of enzyme-substrate recognition. The identification of the response tensor

with the enzyme-substrate complex allows us now to put recognition into the overall dynamical context of catalysis of substrate to product.

### 13. Enzyme Calculus

The mechanism of enzyme-substrate interaction can be represented as



where  $eS$  is the enzyme-substrate complex,  $e'P$  is the “enzyme-product complex”,  $P$  is the product of the interaction, and  $e'$  is the “modified enzyme” from which the enzyme  $e$  can be recovered (by definition of an enzyme being a catalyst). Note that the mechanism (35) is essentially reversible as long as enough energy is present to drive the reaction one way or the other.

Since the left half of Fig. 1(c) is the mathematical analogue of Fig. 4 which represents the left half of mechanism (35), the right half of mechanism (35) should have the right half of Fig. 1(c) as its mathematical analogue. Specifically, let

$$J = LF = \langle a, a \rangle F \tag{36}$$

represent the product  $P$ , then

$$a' = L^{-1}a = \langle a, a \rangle^{-1}a \tag{37}$$

represents the modified (or “dual”) enzyme  $e'$ . Thus the “complex” in the interaction is

$$R = aF = a'J. \tag{38}$$

The process of dual enzyme-product recognition then naturally results from

$$\langle J, a' \rangle = \int Ja' dm. \tag{39}$$

We have, therefore, Fig. 5.

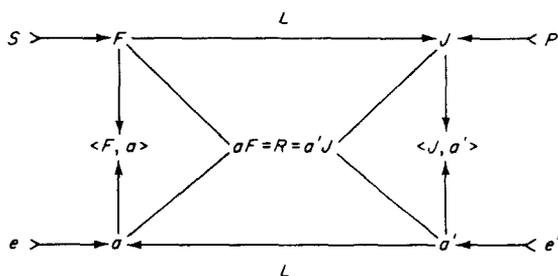


FIGURE 5.

A further comment on equations (36) and (37) is in order. Although  $a = La'$  looks like a linear transformation, which would be a highly idealized, hence unrealistic situation, it in fact is not, because  $L = \langle a, a \rangle$  is a function of  $a$ . Similarly  $J = LF = \langle a, a \rangle F$  is the statement that the transformation from substrate to product is dependent nonlinearly on the enzyme  $a$ .

### 14. Multi-enzyme Systems

Having obtained Fig. 5, we can ask the next question: What happens when we have a collection of several enzymes  $e^1, e^2, \dots, e^m$ ?

Let  $a^1, a^2, \dots, a^m \in L^2(m)$  represent these enzymes, and let them span the description space  $D$ . What do the dynamical interactions in  $D$  represent? For each choice of substrates  $S_1, S_2, \dots, S_m$ , represented by  $F_1, F_2, \dots, F_m \in L^2(m)$  ("inputs"), via the response tensor

$$R = a^i F_i = a_j J^j \tag{40}$$

where

$$J^j = L^{ij} F_i = \langle a^i, a^i \rangle F_i \tag{41}$$

and

$$a^i = L^{ij} a_j, \tag{42}$$

one obtains a collection of products  $P_1, P_2, \dots, P_m$  ("outputs") represented by  $J^1, J^2, \dots, J^m$  (Fig. 6). So  $D$  can be interpreted as a biochemical machine, i.e. a *cell* (or at least the *metabolic* part of a cell).

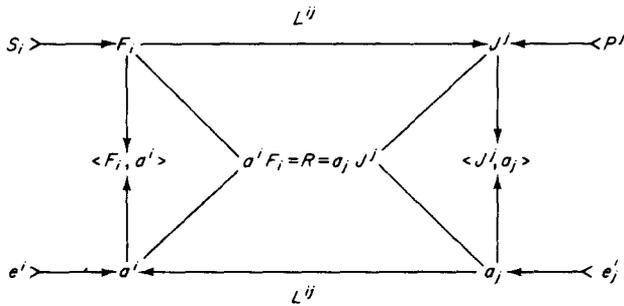


FIGURE 6.

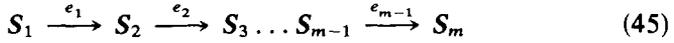
The above represents the case when the enzymes function simultaneously (i.e. in parallel). Suppose we now have the case when

$$a_i = a^{i+1} \tag{43}$$

that is

$$a^i = L^{ii} a^{i+1} = \langle a^i, a^i \rangle a^{i+1} \text{ (no sum)} \tag{44}$$

for  $i = 1, 2, \dots, m - 1$ . Then we have a model of the chain reaction



as depicted in Fig. 7.

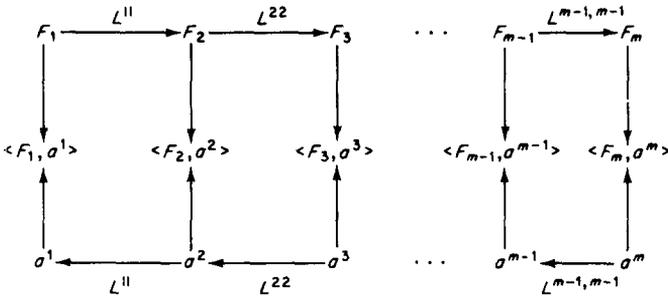


FIGURE 7.

Note there is a major difference between enzymes functioning in parallel and in sequence—in Fig. 6 the interactions between different enzymes ( $L^{ij}$  for  $i \neq j$ ) play a role in the reactions, while in Fig. 7 only the  $L^{ii}$ 's appear.

### 15. Membrane Transport

As regards mechanism, Fig. 6 is equivalent to a schematic diagram for carrier-mediated membrane transport, with the left side corresponding to the exterior of a cell and the right to the interior. The only additional feature of Fig. 6 is the phenomenological description of the process afforded by the metric tensor,  $L^{ij}$ . It must be kept in mind that this phenomenology is not concerned with the dynamics or kinetics of the transport process, but rather describes and relates in a quantitative manner the salient physical structures which the carrier complex uses to recognize and discriminate between the various candidates for transport.

Finally, in order to demonstrate that the proposed phenomenological calculus for recognition processes is not limited to Hilbert description spaces or to enzyme systems, we shall briefly consider passive membrane transport. Passive transport can be described by the linear equations of irreversible thermodynamics as diagrammed in Fig. 1(c) and in particular as given by

equation (1). All that has been said in the previous sections regarding the role of the response tensor in the analysis of recognition processes applies also to the response tensor  $\mathbf{R} = \mathbf{a}^i \mathbf{F}_i$ . There, and also by implication in Edelstein & Rosen (1978), it was shown that the squared norm of the response tensor provides a metric for measuring recognition. It is interesting that for transport processes, the squared norm is identical to the dissipation function,  $\delta$ .

Passive transport is a remarkable example of a phenomenology based upon recognition which is mathematically equivalent to a dynamics based upon a reduction to physical mechanisms. The dyadic response tensor in Fig. 1(c) is an explicit statement about recognition. The summation index  $i$  enumerates the molecular species, and, for each species there is a corresponding constitutive parameter  $\mathbf{a}^i$  which quantifies the membrane system's response to an imposed force,  $\mathbf{F}_i$ . Given this fact of species recognition, all else follows from the three postulates in section 2, even  $\delta \geq 0$ . The unexpected result that  $\delta \equiv |\mathbf{R}|^2 \geq 0$  is a direct consequence of the metrical structure inherent in this calculus for recognition and discrimination, which fundamentally are metrical phenomena.

On the other hand, most dynamic models for transport express the coupling coefficients,  $L^{ij}$ , in terms of Newtonian frictions. The force-flux equations (1) in this case are found directly from the balance of driving forces and frictional forces: see, e.g. Richardson (1970). In such physical models, the condition  $\delta \geq 0$  is provided by the Second Law. Comparing the phenomenological and the dynamical description of transport, we see that the physical mechanism by which a membrane discriminates between molecular species by means of permselectivity is inherent in the constitutive parameters  $\mathbf{a}^i$  since  $L^{ij} = \mathbf{a}^i \cdot \mathbf{a}^j$ .

## 16. Discussion

The reduction of biological problems to physical ones has been a common approach to theoretical biology. The main argument is that physics is the study of matter and its interactions, and that since biological systems are composed of matter, they must be analyzable in terms of the interactions of the particles of which they are composed. Historically, however, the reductionistic approach to biology is frequently too narrow in scope and the investigators often feel that biology stands on a higher hierarchical level than physics. The situation seems to be precisely the converse of the reductionistic idea: far from biology being swallowed up by physics, physics would, rather, be enormously extended by biology.

The representation of the response tensor as a dyadic, a tensor of type (1, 1), is suggested by the mathematical form of the radius vector (R-80).

Vector geometry is of course the mathematical tool used in physics. But what are vectors? They are simply tensors of type  $(0, 1)$  and  $(1, 0)$ . If we agree that biology extends physics, and that biology occupies a higher hierarchical level than physics, then it would be quite reasonable to analyze biological problems using the algebra of tensors of type  $(1, 1)$ , as in our phenomenological calculus. Let us be bold enough to suggest that the response tensor and description space are natural mathematical tools of biology.

A main characteristic of this response tensor approach, as we mentioned before, is that we go directly to the mathematical structure created by interactions. This idea is not foreign to physics. In general relativity, the dynamics of the interactions among gravitating bodies is reduced to the curvature in the metrical structure of spacetime dictated by these bodies—a study of the geometry of a four-dimensional vector (i.e. a tensor of type  $(0, 1)$ ). Analogously, the metrical structure inherent in biological interactions are derivable from the geometry of the (type  $(1, 1)$ ) response tensor.

The concept of the response tensor was originally presented in the context of irreversible thermodynamics (R-80), in terms of the forces and fluxes of the dissipative system of transport processes. Since then the idea has been extended in R-L-S-82 to the analysis of cause-and-effect and aging, and in this paper to the analysis of the problem of recognition, in particular enzyme-substrate interactions, and finally back to the processes of membrane transport. Thus we have gone through a complete cycle. By completing this cycle, we have provided a vigorous, mathematical foundation for a concept which was originally motivated by intuition and physical reasoning and developed primarily by analogy. Having acquired a general foundation, it becomes a general tool.

Let us close by quoting T. S. Eliot from his poem *Little Gidding*:

“And the end of all our exploring  
Will be to arrive where we started  
And know the place for the first time.”

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