

Epistemology and the Role of Mathematics in Translational Science

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Abstract

The terminology “translational science” has recently become very popular; however, there has been little effort to give it an epistemological characterization and thereby give it meaning as a scientific enterprise. This paper takes a step in that direction by recognizing that translational science must begin with the epistemology of science and, rooted in the scientific epistemology, extend that epistemology to encompass human actions in the physical world. The road taken here is to consider the classical understanding of operators on random processes in terms of analysis and synthesis, and to delineate their epistemological domains. The main focus of the paper is on synthesis as translational science, in which synthesis is characterized via operator optimization as opposed to being left to trial and error. Three translational settings are used as illustrations, the unity of these theories within the context of translational science being emphasized: (1) the Wiener-Kolmogorov founding paradigm of optimal linear filters in the context of canonical signal representation, (2) the analogous optimal nonlinear filter theory for images in the context of granulometric spectral representation, and (3) the determination of optimal therapeutic strategies based on structural intervention in gene regulatory networks. The paper closes with some comments on the demands imposed by an epistemologically rigorous approach to translational science.

1 Introduction

If one asks Google to search for the phrase “translational science,” there are more than 100,000 results and, from the tiny sampling I have done for the search-hit leaders, the terminology is almost exclusively applied to medicine; nonetheless, clearly no specific application is inherent in the phrase. If one looks for definitions, these generally have little or no semantic relation to the phrase, even if one restricts attention to “translational biology.” I suspect that a philologist, say, Norbert Wiener’s father, would have a difficult time connecting the phrase “translational science” with both the explicit and implicit definitions being used. One might take the attitude that this lack of attention to rigorous definition is not practically important; however, I believe that this inattention to linguistic rigor is harmful from the perspectives of both knowledge and application. If it is to mean anything, translational science connects scientific knowledge and the application of that knowledge. *Ipsa facto*, if it is to be a meaningful endeavor, then it requires careful epistemological scrutiny.

In recent papers on the epistemology of computational biology and the epistemological crisis in genomics, I have reviewed the scientific epistemology and pointed out how it is being seriously violated in genomic research and, more generally, in bioinformatics [1, 2]. Not only does this inattention to sound epistemology undermine the advancement of science, of necessity it spills over into the translation of science into practical application. Moreover, extending science into translational science, which involves human conceptualization and human-originated action in the physical world, raises new epistemological issues relating to the knowledge of this intentional intervention into the natural order.

In this paper I will focus on translation as pioneered by Norbert Wiener, but which developed quite independently both in the United States and the Soviet Union in the first half of the Twentieth Century. It was

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then that engineering passed from trial and error based upon hunches and adjustments to failure, which could, however inefficiently, translate scientific knowledge into physical action, to a new paradigm of mathematical optimization. This represents an epistemological transformation of engineering, whose business is translation, a transformation that more closely ties engineering to science. Scientific knowledge is translated into practical knowledge by expanding a scientific system to include inputs that can be adjusted to affect the behavior of the system and outputs that can be used to monitor the effect of the external inputs and feed back information on how to adjust the inputs.

2 Modern Science

Because the epistemology of translational science grows out of the scientific epistemology, I begin with the latter, being somewhat brief and referring the interested reader to Hans Reichenbach's *The Rise of Scientific Philosophy* [3], or to [1, 2] for those particularly interested in computational biology.

Aristotelian science came to an end in the Sixteenth Century when Galileo recognized the need for designed experiments – methodological as opposed to unplanned observation. Observations would be made under experimental constraint to elicit specific responses that would be integrated into a system. To quote Reichenbach, “As long as we depend on the observation of occurrences not involving our assistance, the observable happenings are usually the product of so many factors that we cannot determine the contributions of each individual factor to the total result.” [3]. Perhaps Immanuel Kant coined the perfect metaphor for pre-Galilean science when, in the preface of the second edition of the *Critique of Pure Reason*, he wrote, “Reason must approach Nature. . . [as] a judge who compels witnesses to reply to those questions which he himself thinks fit to propose. To this single idea must the revolution be ascribed, by which, after *groping in the dark* for so many centuries, natural science was at length conducted into the path of certain progress.” (my emphasis) [4]

Experiments drive the epistemology of science and the product of an experiment is a set of measurements. These form the empirical basis for knowledge. In themselves, measurements do not constitute scientific knowledge. Scientific knowledge is constituted via synthesis of the observed measurements, which are related to variables and relations among the variables. A system of variables and their relations compose a mathematical model. The model must be mathematical because it relates measurements via numerical structures or judgments via logical constructs. A basic model may be formed by some set of relations, say a stochastic model of a gene regulatory network, but knowledge does not stop there. Mathematical deduction leads to the full knowledge inherent in the relations. In Kantian terminology, the mathematical model constitutes the object of our knowledge. The experiment and the mathematical model form two inseparable requirements for scientific knowledge. Either without the other cannot yield scientific knowledge.

A mathematical model alone does not constitute a scientific theory. The model must be predictive. It must lead to experimental predictions in the sense that there are relations between model variables and observable phenomena such that experimental observations are in accord with the predicted values of corresponding variables. There must be a predictive framework for validation because the truth, or validity, of the model depends on the accuracy of predictions arising from the model. This requires the conceptual system to be related to the experimental methodology. Reichenbach states, “The reference to verifiability is a necessary constituent of the theory of meaning. A sentence the truth of which cannot be determined from possible observations is meaningless. . . The verifiability theory of meaning is an indispensable part of scientific philosophy.” [3]

Prior to the Twentieth Century the abstract symbols of the model were assumed to be measurable in a straightforward manner. However, with the advent of Einstein's general theory of relativity, the terms of the purely mathematical structure no longer refer to the immediate phenomena of human perception as they earlier had. Verification of a system requires that the symbols be tied to observations by some semantic rules that relate not to the general principles of the mathematical model themselves but to conclusions drawn from the principles. In other words, the theory is checked by checking measurable consequences of the theory. These

operational definitions, as they are called, are an intrinsic part of the theory, for without them there would be no connection between the principles and observation. There must be a well-defined procedure for relating the consequences of the equations to quantifiable observations, such as gene expression in the steady state. A scientific theory must have two parts: a structural model and a set of operational definitions for its symbols.

Since a model can only be verified to the extent that its symbols can be tied to observations in a predictive framework, limitations on the ability to design and perform experiments engender limitations on the complexity of a theory. In producing a verifiable theory, the theorist cannot exceed the experimentalist's ability to conceive and perform appropriate experiments, and the experimentalist cannot produce directly meaningful experiments unless they are designed with a symbolic structure in mind. Data mining, which has become very popular, is a throwback to groping in the dark. There is no need to think systematically; just increase the amount of data and something will turn up! Perhaps something will, but what will be its value? And should it have value, how will that value be determined outside some relational (i.e., mathematical) framework? Arturo Rosenblueth and Norbert Wiener write, "An experiment is a question. A precise answer is seldom obtained if the question is not precise; indeed, foolish answers – i.e., inconsistent, discrepant or irrelevant experimental results – are usually indicative of a foolish question." [5]

Mathematics alone is divorced from the empirical basis of science, but without mathematics, meaningful experiments are impossible because scientific meaning is ultimately determined by a set of relationships between a mathematical system and experimental measurements. Indeed, because a model consists of mathematical relations and system variables must be checked against quantitative experimental observations, there is no nonmathematical way to describe the requirements and protocols to assess model validity.

3 Translational Science

If one is going to transform a physical process, then the conceptualization of that physical transformation takes the form of a mathematical operator on some mathematical system, which itself is a scientific model for the state of nature absent the transformation. Although it is possible to model simple systems deterministically, under the assumption that there is negligible variance not explained by the model, more complex systems, especially those which possess unexplained variance owing to important latent variables left out of the model, are typically modeled as random processes, and that is the assumption I will make here (with no exception required for a deterministic model by simply assuming no variation).

There are two basic operator problems concerning random processes. The first basic operator problem is *analysis*: given an operator taking random function inputs, what can be said concerning output statistics in terms of input statistics? If Ψ is an operator on random functions, then our knowledge of Ψ concerns expression of the n th-order distributions of the output random function $\Psi(X)$ in terms of the distributions of the input random function X . For instance, what is the relationship between the input covariance function $K_X(t, t')$ and the output covariance function $K_{\Psi(X)}(s, s')$? The second basic operator problem is *synthesis*: given our desire to transform random functions, can we find some optimal operator, optimality being defined relative to some probabilistic criterion and to whatever constraints are imposed on the operator? For instance, we may desire an operator that filters an observation process to produce an output process that is a best estimate of some unobserved process based on the mean-square error between the processes with the operator constrained to be linear. Analysis and synthesis constitute two different aspects of translational science.

Consider analysis. The input to the operator is a random process describing some phenomenon, such as a stochastic process describing a communication signal or a Markov process describing the evolution of a biological system. The operator Ψ represents some physical operation applied to the input and our scientific knowledge of the output process is constituted by $\Psi(X)$. How the operation is designed is unimportant to our characterization of its effects. One could argue that $\Psi(X)$ may not describe the physical output as well as it could be described by empirically studying and modeling the physical output itself; however, whereas this

approach could involve great time and resources, and be very difficult to accomplish, if Ψ represents well the mathematical effects of the corresponding physical operator, then knowing $\Psi(X)$ eliminates the need for all of that effort. Moreover, and just as importantly, the mapping $X \rightarrow \Psi(X)$, and its analysis, constitutes our conceptual understanding of the physical operation on the input process X .

With synthesis, we use scientific knowledge, in the form of a mathematical system, to build operations that transform the natural world. Unlike analysis, in synthesis it is precisely the design of the operator that is important. Whereas the purpose of science, absent translation, is to gain knowledge of the natural world, translational science is about changing it, and synthesis is the act of designing operations to make those changes. It represents the critical act for human intervention and forms the existential basis of engineering. Rosenblueth and Wiener go so far as to say, “The intention and the result of a scientific inquiry is to obtain an understanding and a control of some part of the universe.” [5] For them, science and translational science are inextricably linked, the ultimate purpose of acquiring scientific knowledge being to translate that knowledge into action. The question is how that translation is to be accomplished. One could proceed in an *ad hoc* manner so that the operator is not derived from the scientific system. In this case, synthesis is not part of translational science; rather, it is a form of groping in the dark, hunting and gathering, where one tries one operation after another in the hope of getting lucky, operator mining instead of data mining. Such groping in the dark does not preclude analysis, and therefore does not preclude translational scientific knowledge. Nonetheless, the critical engineering aspect, that being operator creation for the purpose of transforming nature, is not translational in the scientific sense. For synthesis to be translational requires that the synthesis begin with a mathematical theory that constitutes the relevant scientific knowledge and utilize that theory to arrive at an operator that is optimal, or close to optimal, for accomplishing the desired transformation under the constraints imposed by the circumstances.

Mathematical optimization within the framework of a scientific model does not mean that one can obtain a corresponding physical transformation, but it does provide both a target for physical design and a benchmark for performance. Vladimir Pugachev writes,

The theory of optimal systems (operators) does not enable systems to be found directly which can be embodied forthwith in real constructions. It only enables those mathematical operations on input signals to be determined for which the theoretical limit of accuracy is achieved, for given probability characteristics of the mode of operation and noise, having regard to the nature of the problem and the intrinsic properties of the available data. Accordingly, the practical value of the theory of optimal systems consists mainly in the fact that it makes possible the determination of the theoretical optimum towards which the design engineer must strive in designing a real control system. [6]

It can be argued that modern engineering, which incorporates synthesis into translational science, begins with the optimal time series filtering in the classic work of Andrey Kolmogorov [7, 8] and Norbert Wiener [9]. (Although [9] was published in 1949, an unpublished version appeared in 1942.) One begins with a scientific model and expands the model by adjoining operators with which to desirably alter the behavior of the original system. A criterion exists by which to judge the goodness of the response and the goal is to find an optimal way of manipulating the system. In the classic Wiener-Kolmogorov theory, the scientific model is a signal (stochastic process) and the translational problem is to linearly operate on the signal so as to transform it to be more like some ideal (desired) signal. The synthesis problem is to find an optimal weighting function and the goodness criterion is the mean-square difference between the ideal and filtered signals.

As stated, the translational paradigm is very general. Even if we confine ourselves to filtering a random process, the general paradigm says nothing about the process, nothing about the operator class from which the filter is to come, and nothing about the goodness criterion. Even given the latter, if we make no assumptions regarding the process to be filtered and the filter class, one can only hope for very abstract formulations that may provide no useful form of the solution; indeed, without constraint there may be no optimal solution at all. The less general the system to be operated on and the more constrained the class of allowable operators, the

more likely it is to obtain tractable analytic representations of optimal operators. Moreover, as we will see, a representation of the system (the scientific model) that is compatible with the class of operators over which optimization is to take place is critical for obtaining an analytic solution to the optimization problem.

This paper elucidates the translational paradigm in three settings. The first is the classical Wiener-Kolmogorov optimal linear filtering; however, rather than take the common approach of applying wide-sense stationarity to the Wiener-Hopf equation, I will demonstrate the advantage of proper signal (process) decomposition by utilizing a canonical representation of the signal to arrive at a general solution from which various specialized solutions, including the standard spectral result for wide-sense stationary signals, can be obtained. Next, I will consider optimal nonlinear image filtering and show how a completely parallel process, one based on the proper decomposition of a random set, leads to optimization in the class of granulometric filters. Finally, I will turn to medicine, the place where the terminology "translational science" has become so popular, and consider the problem of finding optimal therapies in the context of gene regulatory networks. Here, the paradigm is the same but the mathematical problem is different in that the model system is a dynamical network and the problem becomes one of transforming a Markov chain. The point will be made that a modern medicine would be translational biology – in this case, translational genomics. Throughout, I will point out the various epistemological aspects of translational science being manifested.

4 Optimal Linear Filters via Canonical Expansions

This section briefly explains Vladimir Pugachev's method of linear optimization via integral canonical expansions [6, 10]. For a more thorough discussion emphasizing the role of image representation, see [11]; for an extensive exposition, see [12].

In the continuous time domain, the basic filtering problem is to estimate an ideal signal $Y(s)$ via an observed signal $X(t)$, where $t \in T$, the domain of observation (which can depend on s). For simplicity, we assume that $X(t)$ has zero mean. A filter Ψ is optimal relative to a probabilistic error criterion ε and a class of operators if

$$\varepsilon[\Psi(X)(s), Y(s)] \leq \varepsilon[\Phi(X)(s), Y(s)] \quad (1)$$

for any Φ in the class. The optimal estimator is denoted by $\hat{Y}(s)$. Herein, the error criterion is the mean-square error (MSE), defined by $E[|\hat{Y}(s) - Y(s)|^2]$. Optimization is over integral linear operators of the form

$$\Psi(X)(s) = \int_T g(s, t) X(t) dt \quad (2)$$

Optimization involves finding $g \in G$, a linear function space on T , to minimize the MSE. If for any $g \in G$, the stochastic integral of Eq. 2 is a random variable having a finite second moment, then \hat{g} yields the optimal MSE linear estimator of $Y(s)$ based on $X(t)$ if and only if it satisfies the *Wiener-Hopf equation*,

$$R_{XY}(s, t) = \int_T \hat{g}(s, u) R_X(u, t) du \quad (3)$$

where R_X and R_{YX} are the autocorrelation and cross-correlation functions for $X(t)$ and for $X(t)$ and $Y(s)$, respectively.

An integral canonical expansion of a random function $X(t)$ takes the form

$$X(t) = \mu_X(t) + \int_{\Xi} Z(\xi) x(t, \xi) d\xi \quad (4)$$

where $Z(\xi)$ is white noise over Ξ (the domain of ξ) and the coordinate functions $x(t, \xi)$ are deterministic. The covariance function of continuous white noise is the generalized function $K_Z(\xi, \xi') = I(\xi) \delta(\xi - \xi')$, where $I(\xi)$ is the intensity of the white noise and the theory of integral representation is interpreted in the generalized sense. Since $X(t)$ has zero mean, we can drop the mean function from the representation. Moreover, $R_X = K_X$.

Integral canonical expansions are formed via a kernel $a(t, \xi)$ by defining

$$Z(\xi) = \int_T X(t) \overline{a(t, \xi)} dt \quad (5)$$

where the overbar denotes the complex conjugate. Three conditions are necessary and sufficient for a canonical expansion to result, one being that

$$x(t, \xi) = \frac{1}{I(\xi)} \int_T a(s, \xi) R_X(t, s) ds \quad (6)$$

where $I(\xi)$ can be expressed in terms of $R_X(t, t')$ and $a(t, \xi)$, and where two other conditions, which we do not state, must hold (see [11] or [12]). Assuming a valid canonical expansion, if it exists, then the optimal linear filter for $Y(s)$ is given by

$$\hat{Y}(s) = \int_T \hat{g}(s, t) X(t) dt \quad (7)$$

$$\hat{g}(s, t) = \int_{\Xi} \frac{\overline{a(t, \xi)}}{I(\xi)} \int_T a(u, \xi) R_{YX}(s, u) du d\xi \quad (8)$$

The optimal linear filter is completely described in terms of the canonical expansion and the second-order moments of the ideal and observed signals.

Suppose $X(t)$ is wide-sense stationary with power spectral density $S_X(\omega)$. If we let $a(t, \omega) = \exp[j\omega t]$ in Eq. 5, then the conditions for a canonical expansion are met, $Z(\omega)$ has intensity $I(\omega) = 2\pi S_X(\omega)$, and $X(t)$ has the integral canonical expansion

$$X(t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} Z(\omega) e^{j\omega t} d\omega \quad (9)$$

Substitution into Eq. 8 and application of the Fourier transform yields the spectral form,

$$\hat{G}(\omega) = S_{YX}(\omega) S_X(\omega)^{-1} \quad (10)$$

of the optimal linear filter [9].

Under the assumption of WS stationarity, it is common to derive Eq. 10 directly from the Wiener-Hopf equation by recognizing that the Wiener-Hopf equation is a convolution. But by seeing Eq. 10 as a special case of Eq. 8, we see that any valid canonical expansion will do and that WS stationarity has the special benefit of making the optimal linear filter depend only on the second moments of the random processes involved.

To go from Eq. 8 to a more specific analytic form requires modeling the autocorrelation and cross-correlation functions. Since filtering is linear, it is not surprising that design can be made more tractable by assuming linear signal models. For instance, in the decomposition of Semenov,

$$X(t) = \sum_{k=1}^n W_k \phi_k(t) + U(t) \quad (11)$$

$$Y(s) = \sum_{k=1}^n W_k \zeta_k(s) + V(s) \quad (12)$$

respectively, where W_1, W_2, \dots, W_n are linearly independent random variables uncorrelated with the zero-mean random functions $U(t)$ and $V(s)$, and $\phi_k(t)$ and $\zeta_k(s), k = 1, 2, \dots, n$, are known deterministic functions [13]. The decomposition is an example of system constraint. Letting $r_{ij} = E[W_i W_j]$ yields

$$R_X(t, t') = \sum_{i=1}^n \sum_{j=1}^n r_{ij} \phi_i(t) \phi_j(t') + R_U(t, t') \quad (13)$$

$$R_{YX}(s, t) = \sum_{i=1}^n \sum_{j=1}^n r_{ij} \zeta_i(s) \phi_j(t) + R_{VU}(s, t) \quad (14)$$

which can represent a significant simplification for $R_X(t, t')$ and $R_{YX}(s, t)$, especially when $U(t)$ and $V(s)$ are easy to describe, for instance, when $U(t)$ is additive noise.

5 Optimal Nonlinear Filters via Granulometric Spectra

During the 1980s there were many papers on nonlinear image processing, especially in morphological image processing, where algorithms were being developed for many image processing tasks. In many cases, there was no postulation of an image class, so that the entire enterprise provided neither scientific nor translational knowledge. In some cases there was legitimate analysis, so that to the extent that the image model was scientifically valid, the analysis provided valid scientific knowledge; however, since generally there was no formulation for operator optimization, synthesis was not translational.

This situation would change in two closely related areas of nonlinear image processing: stack filters and morphological filters. In regard to the latter, there was a growing interest in the representation of image operators that were translation invariant [$\Psi(F + z) = \Psi(F) + z$] and increasing [$F_1 \leq F_2 \Rightarrow \Psi(F_1) \leq \Psi(F_2)$]. This interest was spawned by a theorem of Georges Matheron that provided a representation of such operators in terms of morphological erosions over the kernel of the operator [14] and the reduction of the full kernel representation to a representation over a basis for the kernel [15, 16, 17]. Using the basis expansion for digital images, one could characterize an optimal increasing, translation-invariant operator in terms of finding statistically optimal structuring elements in the erosion expansion [18, 19]. It remained to formulate image models and obtain the optimal structuring elements for these models. While it is possible to derive the optimal operator representation directly in the case of some simple image models, what in fact happened in application was to constrain the class of structuring elements, generate large amounts of simulated data from image models to estimate the structuring elements, and develop efficient algorithms to do so [20].

The situation changed when Gerald Banon and Junior Barrera extended Matheron's theory to any translation-invariant operator by using hit-or-miss transforms instead of erosions [21]. Morphological optimization was quickly put into the new framework [22]. Whereas increasing operators act like low-pass filters, non-increasing filters form a more general class and allow superior filtering in many circumstances, for instance, edge restoration. The downside is that more data are required if the hit-or-miss structuring elements must be estimated from data. This presented a problem in practice even when tens of thousands of images could be simulated. It required further constraints on the space of structuring elements and more efficient methods, but in practice proved to be valuable for situations in which the constraints were compatible with image structure [23]. In subsequent years various image-related optimization constraints and efficient implementations were developed.

Whereas morphological optimization was focused on filter expansions, the class of stack filters was being characterized via a principle of superposition. In fact, stack filters are morphological in the sense that they form a special class of gray-scale increasing, translation-invariant digital filters for which the basis structuring elements are flat [16], but that was not the main focus of the research. In any event, there was significant interest in estimation-based optimization of stack filters [24, 25]. Subsequently, progress was made on model-based optimization of stack filters for simple signal-noise models [26, 27]. Regarding stack filter optimization, in 1999 Jaakko Astola and Pauli Kuosmanen wrote,

In the theory of linear systems, the power spectrum of the input signal together with the transfer function of the system determines the power spectrum of the output signal. It is not possible to get equally simple strong connections between the input process and the output process for stack filters. Explicit information on the statistical properties of the output can only be derived for the case of

constant signal plus noise. Even then we need to assume the noise to be white. However, this result makes possible numerical optimization of noise attenuation of stack filters under different conditions, which guarantee that the filter satisfies prescribed specifications. [28]

There are three key points in this statement: (1) a signal model can be postulated for which analytic results can be obtained; (2) the model is much simpler than that which can be obtained for linear filters; and (3) nonetheless, it is useful for understanding the behavior of stack filters.

As can be gleaned from these remarks, filter optimization falls into the general translational paradigm. The image model is a random process and represents our mathematical understanding of the corresponding physical process, whose empirical basis is formed via measurements, in the continuous case this being the analog measurements and in the digital case this being the pixel intensities. From a strictly scientific perspective, the image model, which is a mathematical construct, constitutes scientific knowledge and its validity is judged by how well it predicts future captured images; however, when designing image filters we are addressing the translational question.

The vast majority of work on the optimization of nonlinear filters, although within the translational paradigm, is quite different from the Wiener-Kolmogorov theory. There, the optimal filter is deduced from the mathematical formulation of the relevant processes and operators, whereas nonlinear filter design has mainly been accomplished by generating synthetic data from the model and then estimating the relevant parameters defining the optimal operator. Filters are generally defined over a finite digital window, so that they involve optimization of a discrete-valued function defined on a random vector of finite dimensions and thus filter design can be placed into the domain of pattern classification, the filter classifying the value of the point at the window origin [29].

In this section I discuss a class of nonlinear filters based on morphological openings for which analytic optimal filter design can be achieved with a kind of spectral approach analogous to the Wiener-Kolmogorov theory. The idea was suggested to me by Robert Haralick and was based on the intuitive notion of an opening structuring element acting like a rolling ball inside a binary image. As the ball grows, it will sweep away ever more image components. In early papers, we considered several kinds of “spectra” but all proved to be too simple [30, 31, 32]; nonetheless, one of these, the shape-based opening spectrum, although it was inadequate for a satisfactory theory, was on the right track. Just as the power spectrum was compatible with linear filters, we needed a spectrum compatible with opening-type filters. After some time, I recognized that Pugachev’s theory of canonical-expansion-based filter design held the key, that more attention had to be paid to image representation and proper image decomposition, that filter design would require careful topological and measure-theoretic considerations to arrive at a satisfactory theory, and that Matheron had laid some key ground work in his theory of granulometries [14]. The way was clear to a geometric spectral theory in which to characterize optimal granulometric filters [33], as well as adaptive granulometric filters [34]. From the perspective of the current paper, to translate science (the image model) required the proper model representation, a compatible filter class, and an understanding of the relation between the model and operator representations. Here I will briefly outline the theory, leaving the mathematical issues to the literature.

A granulometry is a set-operator family $\{\Psi_t\}, t > 0$, such that Ψ_t is increasing, antiextensive [$\Psi_t(S) \subset S$], translation invariant, and $\Psi_t \Psi_s = \Psi_s \Psi_t = \Psi_{\max(t,s)}$. We define $\Psi_0(S) = S$. As t increases, the volume of $\Psi_t(S)$ decreases. The most commonly used granulometry is

$$\Psi_t(S) = \bigcup_{i=1}^n S \circ tB_i \quad (15)$$

where the *generator* $\{B_1, B_2, \dots, B_n\}$ is a collection of compact, convex sets and $S \circ tB_i$ is the morphological opening of S by tB_i . This granulometry distributes over disjoint collections of compact sets, meaning that, if S_1, S_2, \dots, S_m are mutually disjoint and compact, then Ψ_t applied to the union of S_1, S_2, \dots, S_m equals the union of $\Psi_t(S_1), \Psi_t(S_2), \dots, \Psi_t(S_m)$. We assume distributive granulometries.

Given a random set S and letting ν denote Lebesgue measure (volume), the *granulometric size distribution* for S is defined by

$$\Omega_S(t) = \nu(S) - \nu(\Psi_t(S)) \quad (16)$$

[14]. Ω_S is a random function relative to the random set S . Let $M_S(t)$ denote the mean of $\Omega_S(t)$, absent normalization for unit integral. $M_S(t)$ is increasing in t and $M_S(0) = 0$. The derivative H_S of M_S is called the *granulometric size density* (GSD). We assume M_S is of bounded variation and continuous from the left. Then M_S is continuous except on at most a countable set, M_S is differentiable a.e., H_S is integrable, and M_S possesses the Lebesgue decomposition $M_S(t) = K_S(t) + A_S(t)$, where K_S is increasing, $K_S'(t) = 0$ a.e., A_S is increasing, A_S is absolutely continuous, A_S is differentiable a.e., and $A_S(t)$ is obtained by integrating M_S from 0 to t .

The *granulometric spectrum* of S relative to $\{\Psi_t\}$ is defined for $t \geq 0$ by

$$S_t = \bigcap_{h>0} \Psi_t(S) - \Psi_{t+h}(S) = \Psi_t(S) - \bigcup_{h>0} \Psi_{t+h}(S) \quad (17)$$

[33]. The spectral components S_t partition S . For every t -interval I , there is a spectral band $G_S(I) = \bigcup_{t \in I} S_t$. A countable-interval subset of $[0, \infty)$ is a subset $\Pi \subset [0, \infty)$ that can be expressed as a countable union of disjoint intervals Π_i , where single points are intervals of length zero, and $i < j$ implies Π_i is left of Π_j and Π_i and Π_j are separated by Π^c . If Π is a countable-interval subset, then the *granulometric bandpass filter* Λ_Π is defined by

$$\Lambda_\Pi(S) = \bigcup_{t \in \Pi} S_t = \bigcup_{i=1}^{\infty} G_S(\Pi_i) \quad (18)$$

where the second union may be finite. Π and Π^c are the *pass* and *fail* sets for Λ_Π .

The signal-union-noise model consists of a signal random set S , noise random set N , and observed set $S \cup N$. We assume that the signal and noise are disjoint. An optimal bandpass filter is one that minimizes the MSE of $\Lambda_\Pi(S \cup N)$ as an estimator of S . In the commonplace special case when $M_S(t)$ and $M_N(t)$ have no singular parts, then the *optimal granulometric bandpass filter*, $\Lambda_{\Pi(\Psi)}$, is defined by the pass set

$$\Pi(\Psi) = \{t : H_S(t) \geq H_N(t)\} \quad (19)$$

where, if either derivative fails to exist or the derivatives are equal at t , then the choice of pass or fail set for t is irrelevant (and a more general formulation exists when the size distribution means possess singular parts) [33]. Certain spectral bands are passed and others are not according to the inequality involving the granulometric size densities.

The entire procedure works because the image decomposition is compatible with the filter structure. It results from viewing the image from a granulometric perspective when applying a granulometric filter. This is akin to the linear situation in which the signal is viewed from a covariance perspective, which is precisely the perspective relevant to linear filtering. Indeed, there is a striking similarity between Eqs. 10 and 19. In Eq. 19, a spectral component is passed in full depending on whether $H_S(t) \geq H_N(t)$. If we were to binarize the transfer function in Eq. 10 by thresholding at $1/2$, then a frequency ω would contribute in full or not at all, depending on whether $S_{YX}(\omega) \geq S_X(\omega)$. If we assume that the observation $X(t)$ is signal $Y(t)$ plus uncorrelated noise $N(t)$, then this inequality becomes

$$S_Y(\omega) \geq S_N(\omega) \quad (20)$$

which looks much like Eq. 19.

Analogous to the linear case (Eqs. 11,12,13,14), specialized results are obtained by making stronger image and filter assumptions. For instance, granulometry $\{\Phi_t\}$ results from granulometry $\{\Psi_t\}$ by *reconstruction*

if for each connected component V in a set, $\Phi_t(V) = V$ if $\Psi_t(V) \neq \emptyset$ and $\Phi_t(V) = \emptyset$ if $\Psi_t(V) = \emptyset$. For a *reconstructive granulometry* $\{\Phi_t\}$ and a random connected compact set V , the *granulometric measure* of V relative to $\{\Phi_t\}$ is defined by $\lambda(V) = \sup\{t : \Phi_t(V) = V\}$. It is a random variable depending on the distribution of V . Consider the random set

$$S = \bigcup_{k=1}^m S_k + z_k \quad (21)$$

where S_1, S_2, \dots, S_m are identically distributed to a primary random compact grain S_0 , m is a random positive integer independent of S_0 , z_1, z_2, \dots, z_m are locations randomized up to disjointness, and the primary grain S_0 depends on a random parameter vector \mathbf{W} possessing multivariate density $f_{\mathbf{W}}(\mathbf{w})$. Then, relative to $\{\Phi_t\}$, it can be shown that

$$H_S(t) = \int_{\{\mathbf{w}: \lambda[S_0(\mathbf{w})] < t\}} \lambda[S_0(\mathbf{w})] f_{\mathbf{W}}(\mathbf{w}) d\mathbf{w} \quad (22)$$

In certain situations this integral can be sufficiently tractable that $H_S(t)$ can be obtained. Using a similar approach for the noise can yield analytic determination of the optimal bandpass filter, where for disjoint grains the noise is viewed as clutter [34].

6 Translational Genomics: Intervention in Gene Regulatory Networks

The intent of the preceding sections has been to elucidate translational science in the context of signal filtering and to show how a proper appreciation of a fundamental paradigm can lead to the analogous treatment of related problems. This section will return to where we started: medicine. The science to be translated is genomics, the framework is genomic signal processing, and the goal of the translation is to provide therapeutic strategies based on controlling gene regulation. The problem considered here is different in two ways. First, the scientific model is not a stochastic time series or random set, but a dynamical network whose probabilistic description is characterized via a Markov chain and, second, the translational problem will be to alter the steady-state distribution of the network.

Owing to the multivariate manner in which genes govern cellular function, including their regulatory effects on each other, the modeling of gene regulatory networks is a salient issue in systems biology. Appropriate network modeling is critical to understanding the manner in which cells execute and control the enormous number of operations required for normal function and the ways in which cellular systems fail in disease. Many approaches to modeling gene regulatory networks have been proposed, each with its own assumptions, data requirements, and goals, including linear models, Bayesian networks, neural networks, nonlinear ordinary differential equations, stochastic logical networks, and graph-based models (see [35, 36] for reviews).

A fundamental goal of translational genomics is to develop therapies based on the disruption or mitigation of aberrant gene function contributing to the pathology of a disease. Mitigation would be accomplished by the use of drugs to act on the gene products. The salience of drug-based therapy can be seen in one of the proposed definitions for translational science in the context of medicine: "the application of biomedical research (pre-clinical and clinical), conducted to support drug development, which aids in the identification of the appropriate patient for treatment (patient selection), the correct dose and schedule to be tested in the clinic (dosing regimen) and the best disease in which to test a potential agent (disease segment)." [37]

Translational intervention involves constructing nonlinear dynamical networks (mathematical models) characterizing gene regulation and synthesizing intervention strategies to optimally modify the dynamical behavior of these networks [38, 39, 40]. Translational intervention has been studied mainly in the framework of Probabilistic Boolean Networks (PBNs) [41, 42]. The PBN model is a generalization of the classical Boolean network model introduced by Stuart Kauffman in the late 1960s [43, 45]. PBNs extend the original Boolean network

model by incorporating uncertainty in the functions governing network transitions, whether uncertainty arises from inherent biological considerations, model constraint, or inference from data.

The first intervention strategy considered for gene regulatory networks, in particular, for binary PBNs, considered the following problem: given the network is in an undesirable state, determine the optimal single-gene flip to move it to a desirable state as early as possible [44]. Under this scenario, the intervention is transient and does not affect the long-run dynamics of the network.

Following this first effort, two distinct intervention paradigms have been considered: (1) using external control variables to affect the transition probabilities of the network and thereby affect its dynamic evolution [46, 47] and (2) altering the structure (wiring) of the network [48, 49, 50]. The first approach, external control, uses the fact that the dynamic behavior of the PBN can be modeled by a Markov Chain, thereby making the PBN amenable to the theory of Markov decision processes and finding optimal solutions by dynamic programming. In the case of finite-horizon external control, the effects are transient and the steady-state distribution is not changed, whereas in infinite-horizon external control it is changed (see [51] for a review). In this paper, the focus is on the second approach, referred to as *structural intervention*. Structural changes alter the steady-state distribution. Given a class of potential structural changes, the problem is to find the optimal structural intervention relative to a desired alteration of the steady-state distribution.

A binary *Boolean network* (BN) on n genes is defined by a truth table giving the functional relationships between genes. Each gene $x_i \in \{0, 1\}$ at time $t + 1$ is determined by the values of some predictor genes at time t via a Boolean function $f_i: \{0, 1\}^{K_i} \mapsto \{0, 1\}$ in the truth table, where K_i is the number of predictor genes for x_i in the network. At any time t , the state of the network is defined by a state vector $\mathbf{x}(t) = (x_1(t), x_2(t), \dots, x_n(t))$, called a *gene activity profile* (GAP). Given an initial state, a BN will eventually reach a set of states, called an *attractor cycle*, through which it will cycle endlessly. Each initial state corresponds to a unique attractor cycle and the set of initial states leading to a specific attractor cycle is known as the *basin of attraction* (BOA) of the attractor cycle.

Perturbation is introduced with a positive probability p by which the current state of the network can be randomly changed, thereby defining a *Boolean network with perturbation* (BNp). Implicitly, we assume that there is an i.i.d. random perturbation vector $\gamma \in \{0, 1\}^n$, where the i th gene flips if the i th component of γ is equal to 1. Hence, $p = P\{\gamma_i = 1\} = E[\gamma_i]$ is the same for all the genes. If $\mathbf{x}(t)$ is the GAP at time t , then the next state $\mathbf{x}(t + 1)$ is either $\mathbf{f}(\mathbf{x}(t))$ with probability of $(1 - p)^n$ or $\mathbf{x}(t) \oplus \gamma$ with probability $1 - (1 - p)^n$, where \mathbf{f} is the multi-output function from the truth table and \oplus is component-wise addition modulo 2. Introduction of perturbation makes the corresponding Markov chain of a BNp irreducible and ergodic. Hence, the network possesses a steady-state distribution π describing its long-run behavior. A BNp inherits the attractor structure from the original Boolean network without perturbation, the difference being that a random perturbation can cause a BNp to jump out of an attractor cycle, perhaps then transitioning to a different attractor cycle prior to another perturbation. If p is sufficiently small, then π will reflect the attractor structure within the original network. We can derive the transition probability matrix P if we know the truth table and the perturbation probability p for a BNp.

A binary *probabilistic Boolean network* (PBN) is composed of a family $\{B_1, B_2, \dots, B_m\}$ of BNps together with probabilities governing the selection of a BNp at each time. The m constituent BNps are characterized by m network functions, $\{\mathbf{f}_1, \mathbf{f}_2, \dots, \mathbf{f}_m\}$. At any time point there is a positive probability q of switching from the current governing constituent BNp to another. By definition, a PBN inherits the attractor cycles of its constituent BNps. There are two modeling interpretations regarding q . If $q < 1$, the interpretation is that there are latent variables outside the network whose changes cause the model network to behave stochastically, the PBN is said to be *context-sensitive* [52], and q is usually assumed to be small, reflecting the assumption that the BNp governing network dynamics is only changed infrequently. If $q = 1$, as in the original formulation of PBNs [41], then the interpretation is that the uncertainty in the BNp arises from uncertainty in model inference and the PBN is said to be *instantaneously random*.

In the present framework, a function perturbation is a change to one of the Boolean functions and a structural

intervention is a change to the truth table governing network transitions via a function perturbation (the term "perturbation" being used in two different senses in this paper). To find an optimal structural intervention we need to determine the long-run effect of such a perturbation. Following function perturbation the original transition matrix P and steady-state distribution π are changed to \tilde{P} and $\tilde{\pi}$, respectively. Our desire is to represent $\tilde{\pi}$ in terms of π and P so that an optimal perturbation can be determined directly from π and P . Some basic results are provided here; see [50] for the full study.

With perturbation, the dynamics of a BNp can be analyzed as a homogeneous irreducible finite Markov chain \mathbf{X}_t with the state space $\{0, 1\}^n$. The state transitions of a BNp over time are governed by the transition rules \mathbf{f} and γ . For each pair of states \mathbf{x} and \mathbf{y} , the transition probability $P_{\mathbf{y}}(\mathbf{x}) = P[\mathbf{X}_{t+1} = \mathbf{x} | \mathbf{X}_t = \mathbf{y}]$ from \mathbf{y} to \mathbf{x} at time t is given by

$$P_{\mathbf{y}}(\mathbf{x}) = \mathbf{1}_{[\mathbf{f}(\mathbf{y})=\mathbf{x}]}(1-p)^n + \mathbf{1}_{[\mathbf{x} \neq \mathbf{y}]}p^{\eta(\mathbf{x},\mathbf{y})}(1-p)^{n-\eta(\mathbf{x},\mathbf{y})}, \quad (23)$$

where $\mathbf{1}_{[\mathbf{f}(\mathbf{y})=\mathbf{x}]} = 1$ if $\mathbf{f}(\mathbf{y}) = \mathbf{x}$ according to the truth table and $\mathbf{1}_{[\mathbf{f}(\mathbf{y})=\mathbf{x}]} = 0$ otherwise, and $\eta(\mathbf{x}, \mathbf{y})$ is the Hamming distance between \mathbf{x} and \mathbf{y} . Based on this, we can derive the transition probability matrix P of the underlying Markov chain by computing all of its entries. More general expressions exist for instantaneously random and context-sensitive PBNs [50].

The basic idea is to derive $\tilde{\pi}$ for PBNs based on the results for general Markov chains. For the original and perturbed networks, $\pi^T P = \pi^T$ and $\tilde{\pi}^T \tilde{P} = \tilde{\pi}^T$, where T denotes transpose. Analytical expressions for the steady-state distribution change can be obtained using the fundamental matrix, which exists for any ergodic Markov chain and is given by $Z = [I - P + e\pi^T]^{-1}$, where e is a column vector whose components are all unity [53]. While various results can be obtained in the general setting, interest here is with special cases that apply to PBNs; in particular, we want to express $\tilde{\pi} - \pi$ without reference to $\tilde{\pi}$. Letting $\tilde{P} = P + E$, the steady-state distribution change is

$$(\tilde{\pi} - \pi)^T (I - P) = \tilde{\pi}^T E. \quad (24)$$

For a *rank-one perturbation*, the perturbed Markov chain has the transition probability matrix $\tilde{P} = P + ab^T$, where a, b are two arbitrary vectors satisfying $b^T e = 0$, and ab^T represents a rank-one perturbation to the original transition probability matrix P . In this case, it can be shown that

$$\tilde{\pi}^T = \pi^T + \frac{\pi^T a}{1 - b^T Z a} b^T Z, \quad (25)$$

[54] (see [50] for details). An important special case occurs when the transition mechanisms before and after perturbation differ only in one state, say the k th state. Then $E = e_k b^T$ has non-zero values only in its k th row, where e_k is the elementary vector with a 1 in the k th position and 0s elsewhere. Substituting this into Eq. 25 yields

$$\tilde{\pi}^T = \pi^T + \frac{\pi^T e_k}{1 - b^T Z e_k} b^T Z = \pi^T + \frac{\pi_k}{1 - \beta_k} \beta \quad (26)$$

where $\beta^T = b^T [I - P + tu^T]^{-1}$ [53]. For the i th state,

$$\tilde{\pi}_i = \pi_i + \frac{\pi_k \beta_i}{1 - \beta_k}. \quad (27)$$

The results for these special cases can be extended to arbitrary types of perturbations so that it is possible to compute the steady-state distributions of arbitrarily perturbed Markov chains in an iterative fashion [50]. For complicated perturbations, the computation for the iterative algorithm is in the form of vector-matrix multiplication and the complexity of the procedure increases linearly with the increasing number of perturbations.

To accomplish optimal intervention in PBNs, these general Markov chain results must be adapted to PBNs. Consider the case of a single perturbation on a BNp, which is a flip for one target gene at the response side

for the predictor state k in the truth table. Ignoring perturbation, each row in the transition probability matrix corresponds to a single input state i and the row consists of all 0s except for a 1 in the column of the output state $\mathbf{f}(i)$. A one-bit perturbation for input state k means that there is a network function transformation $\mathbf{f} \rightarrow \tilde{\mathbf{f}}$ with $v = \tilde{\mathbf{f}}(k) \neq \mathbf{f}(k) = u$ and $\tilde{\mathbf{f}}(i) = \mathbf{f}(i)$ for all $i \neq k$. Hence, there is now (with $\tilde{\mathbf{f}}$) a 1 in the column of the output state v and a 0 in the column of state u , whereas originally (with \mathbf{f}) there was a 0 in the column of the output state v and a 1 in the column of state u , and all other entries in the matrix are unchanged. Relative to the BNp, this changes the transition probability matrix P only at p_{ku} and p_{kv} . Thus, $\tilde{p}_{ku} = p_{ku} - \tau$ and $\tilde{p}_{kv} = p_{kv} + \tau$, where τ is decided by the change to the truth table and the perturbation probability p . Given these changes, it can be shown via Eq. 27 that

$$\tilde{\pi}_i = \pi_i + \frac{(1-p)^n \pi_k (z_{vi} - z_{ui})}{1 - (1-p)^n (z_{vk} - z_{uk})}. \quad (28)$$

where z_{vi} is the (v, i) entry in the fundamental matrix Z . This scheme can be extended to more sophisticated function perturbations, to instantaneously random PBNs, and to context-sensitive PBNs, albeit, with increasing complexity [50].

The objective of intervention is to keep cells away from certain states (for example, metastatic cancerous phenotypes). The goal of structural intervention is to alter the long-run dynamics of the network by altering the rule structure. Given a set \mathcal{U} of undesired states, we want to minimize $\sum_{i \in \mathcal{U}} \hat{\pi}_i$ over all structural changes within a given class. This can be done analytically using the fact that $\hat{\pi}_i$ can be expressed in terms of π_i , the difference vector for the k th rows of the transition matrices, and the fundamental matrix (Eq. 27). One can constrain the optimization in many ways, for instance, by limiting the amount of mass in any given state. One might also put limits on the change in mass $|\hat{\pi}_i - \pi_i|$ of some states, so that there is no over concentration of mass in certain states of the altered network.

An application from [50] is now used to illustrate optimal structural intervention in an instantaneously random PBN. It involves a model of the mammalian cell cycle proposed in [55], which was previously used for the study of optimal infinite-horizon external control [56]. In the wild-type cell-cycle model for a normal mammalian organism, cell division should coordinate with overall growth. This process is tightly controlled by extra-cellular signals that indicate whether a cell should divide or remain in a resting state. The positive signals, or growth factors, instigate the activation of Cyclin D (CycD), a key gene in the mammalian cell cycle. Two other important genes are retinoblastoma (Rb) and p27. Rb is a tumor-suppressor gene expressed in the absence of the cyclins, which inhibit Rb by phosphorylation. Gene p27 is also active in the absence of the cyclins. Whenever p27 is present, it blocks the action of CycE or CycA and Rb can also be expressed, even in the presence of CycE or CycA. Hence, it stops the cell cycle. Following a proposed mutation in [56], we assume p27 is mutated and is always off. In this cancerous scenario, p27 can never be activated. This mutation introduces a situation where both CycD and Rb might be inactive. As a result, in this mutated phenotype, the cell cycles in the absence of any growth factor. Thus, we consider the logical states in which both Rb and CycD are down-regulated as undesirable states, when p27 is mutated.

We use the PBN that postulates the cell-cycle with mutated phenotype. Table 1 summarizes the mutated Boolean functions derived from the functions given in [55]. We construct the instantaneously random PBN of the cell cycle based on the Boolean functions in Table 1. This PBN consists of 9 genes: CycD, Rb, E2F, CycE, CycA, Cdc20, Cdh1, UbcH10, and CycB. The above order of genes is used in the binary representation of the logical states, with CycD as the most significant bit and CycB as the least significant bit. The order of genes in the logical states does not affect intervention. We assume that the extra-cellular signal to the cell-cycle model is a latent variable. The growth factor is not part of the cell and its value is determined by the surrounding cells. The expression of CycD changes independently of the cell's content and reflects the state of the growth factor. Depending on the expression status of CycD, two constituent Boolean networks are obtained. The first constituent Boolean network is determined from Table 1 when CycD = 0; the second constituent Boolean network is determined by CycD = 1. To completely define the PBN, we set the perturbation probability $p = 0.01$

Table 1: Definitions of Boolean functions for the cell cycle PBN

Order	Gene	Regulating function
x_1	<i>CycD</i>	extra-cellular signals
x_2	<i>Rb</i>	$(\overline{CycD} \wedge \overline{CycE} \wedge \overline{CycA} \wedge \overline{CycB})$
x_3	<i>E2F</i>	$(\overline{Rb} \wedge \overline{CycA} \wedge \overline{CycB})$
x_4	<i>CycE</i>	$(E2F \wedge \overline{Rb})$
x_5	<i>CycA</i>	$(E2F \wedge \overline{Rb} \wedge \overline{Cdc20} \wedge (\overline{Cdh1} \wedge \overline{UbcH10})) \vee (CycA \wedge \overline{Rb} \wedge \overline{Cdc20} \wedge (\overline{Cdh1} \wedge \overline{UbcH10}))$
x_6	<i>Cdc20</i>	<i>CycB</i>
x_7	<i>Cdh1</i>	$(\overline{CycA} \wedge \overline{CycB}) \vee \overline{Cdc20}$
x_8	<i>UbcH10</i>	$\overline{Cdh1} \vee (\overline{Cdh1} \wedge \overline{UbcH10} \wedge (\overline{Cdc20} \vee CycA \vee CycB))$
x_9	<i>CycB</i>	$(\overline{Cdc20} \wedge \overline{Cdh1})$

Table 2: $\sum_{x_1=0, x_2=0} \tilde{\pi}(\mathbf{x})$ with the optimal 1-bit function perturbations for all f_i s in the cell cycle PBN.

Gene	Rb	E2F	CycE	CycA	Cdc20	Cdh1	UbcH10	CycB
BN_1	0.1350	0.2064	0.1882	0.2028	0.1703	0.2134	0.2160	0.2190
BN_2	0.0317	0.0505	0.1842	0.2042	0.2330	0.2083	0.2064	0.2221

and the probability of selecting each constituent Boolean network $c_j = 0.5, j = 1, 2$.

In this cancerous scenario the goal is to avoid the logical states with simultaneously down-regulated CycD and Rb. Thus, we aim to steer the network dynamics away from these undesirable states, where $x_1 = 0$ and $x_2 = 0$. We desire the optimal one-bit function perturbation to hinder cell growth and minimize $\sum_{x_1=0, x_2=0} \tilde{\pi}(\mathbf{x})$, the undesirable steady-state mass for the original network being 0.216. We check all possible functions to find the one perturbation that minimizes this objective function and is also practically controllable. Table 2 shows the objective function values with the optimal one-bit function perturbations, respectively, for each f_i in the two constituent Boolean networks. Note that perturbation to the wrong gene can increase the undesirable mass. As CycD is determined by extra-cellular signals, we cannot perturb it and therefore the table does not have CycD included. The table shows that the perturbations to the function regulating Rb significantly reduce the steady-state mass of the undesirable states. Flipping the output expression in the truth table for the second Boolean network leads to the minimum objective function value. Hence, in practice, our choice is to intervene with the function regulating Rb to shift the stationary mass away from undesirable states.

7 Concluding Comments

Three examples of translational science have been presented, each representing a different level of approach to translation. The first, optimal linear filtering, due to two of the greatest minds of the Twentieth Century, lays down an entirely new paradigm with far reaching effects and requires a substantial mathematical effort. The second results from observing parallels with an existing paradigm, in this case the Wiener-Kolmogorov theory in the framework of canonical signal expansion, and requires some new mathematics to provide the analogous structure in a different environment. The third, which perhaps is the most common translational approach, recognizes the proper structural setting for the application within an existing mathematical theory and places the application into that setting by particularizing the general mathematical analysis to the problem at hand. The three problems may represent different approaches to translation, but they are unified. Their unity is that, just as

basic scientific knowledge is constituted in mathematical systems, so too is translational scientific knowledge as it seeks to extend basic scientific knowledge.

One can go further by claiming a unity in the problems themselves. It might seem easy to argue that nonlinear image processing and linear signal processing share a lot in common, but they differ in two major ways. First, nonlinear analysis lacks the unifying structure of linear spaces and, second, two-dimensional random processes are much more difficult to deal with than one-dimensional processes, both probabilistically and topologically. Yet one could at least argue that there is a significant domain of intersection. On the other hand, it might seem easy to argue that nonlinear image processing is a long way from the control of gene regulatory networks and systems biology. In fact, there are many structural similarities, not the least of which is that the modeling of biological processes depends on the theory of stochastic multivariate nonlinear systems, as does image processing. In fact, the three problems I have chosen are epistemologically close.

But one can go much further, and Norbert Wiener does. In 1948 he wrote, “Thus, as far back as four years ago, the group of scientists about Dr. Rosenblueth and myself had already become aware of the essential unity of the set of problems centering about communication, control, and statistical mechanics, whether in the machine or in living tissue.” [57] Wiener had grasped the epistemological unity of systems and translational science concerning systems – whether it be electrical systems and communications theory or biological systems and medical theory. To miss this unity is to go back before the time of Wiener and to greatly limit what can be accomplished in translational research.

To manifest this unity will require a radical change in the way research and education are carried out. As the problems we face become more complex, which typically means that the stochastic systems become more complex and exhibit greater nonlinearity. we require researchers with ever greater education in mathematics, and not the relatively easy linear mathematics typical of engineering education. One requires rigorous mathematical training in areas such as measure theory, topology, probability theory, and stochastic processes before even approaching stochastic nonlinear dynamical systems. There is very little intuition when it comes to the behavior of these systems. One depends on the mathematics. And the mathematics of medicine will dwarf the mathematics of electrical engineering.

I believe that Wiener recognized the difficulties that the mathematical requirement of science and translational science would present for medicine when he wrote the following words:

It is these boundary regions of science which offer the richest opportunities to the qualified investigator. They are at the same time the most refractory to the accepted techniques of mass attack and the division of labor. If the difficulty of a physiological problem is mathematical in essence, ten physiologists ignorant of mathematics will get precisely as far as one physiologist ignorant of mathematics. If a physiologist who knows no mathematics works together with a mathematician who knows no physiology, the one will be unable to state his problem in terms that the other can manipulate, and the second will be unable to put the answers in any form that the first can understand. Dr. Rosenblueth has always insisted that a proper exploration of these blank spaces on the map of science could only be made by a team of scientists, each a specialist in his own field but each possessing a thoroughly sound and trained acquaintance with the fields of his neighbors; all in the habit of working together, of knowing one another’s intellectual customs, and of recognizing the significance of a colleague’s new suggestion before it has taken on a full formal expression. The mathematician need not have the skill to conduct a physiological experiment, but he must have the skill to understand one, to criticize one, and to suggest one. The physiologist need not be able to prove a certain mathematical theorem, but he must be able to grasp its physiological significance and tell the mathematician for what he should look. [57]

Wiener’s words go beyond medicine to any field requiring sophisticated mathematical modeling, in particular, random processes. They characterize an epistemological necessity for the advancement of knowledge,

the functional knowledge of science, not just the gathering of data points, the meaningless output of some data-mining program, or the subjective satisfaction of an explanation.

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