Medicine beyond magic bullets: a formal case for multilevel interventions

Rodrick Wallace
Division of Epidemiology
The New York State Psychiatric Institute*

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Abstract

Western medicine's paradigmatic search for 'magic bullet' interventions is facing increasing difficulty: Between 1950 and 2010 the inflation-adjusted research cost per USFDA-approved drug has increased exponentially in time, an draconian inverse of the famous Moore's Law of computing. A sequence of empirically-oriented statistical models suggests that carefully designed synergistic multifactorial and multiscale strategies might evade this relationship.

Key Words: cost containment, public policy, synergism, translational medicine

1 Introduction

Western medicine's relentless culturally-determined hunt for simple magic bullets against complex multifactorial chronic and infectious disease is coming to an end as biologically simple low-hanging fruit is picked off and as pathogens evolve out from under existing antibiotics. Figure 1, adapted from Bernstein, (2010), shows the number of small molecule and biologic USFDA approvals per inflation-adjusted billion dollars in research investment between 1950 and 2010. The cost per intervention has increased from about $ 200 million to over $ 1.2 billion, and many pharmaceutical firms have markedly cut their research efforts.

Paul et al. (2010) summarize the crisis as follows:

> [W]ithout a dramatic increase in [Research and Development] productivity, today's pharmaceutical industry cannot sustain sufficient innovation to replace the loss of revenues due to patent expirations for successful products... [However].. a more complete understanding of human (disease) biology will... be required before many true breakthrough medicines emerge.

Here we will outline a kind of statistical theory of biological interaction that might significantly improve our understanding of human disease biology and contribute to altering the form of figure 1, a depressing inverse medical parallel to the famous Moore's Law that has characterized the doubling of on-chip computing power every two years since 1971.

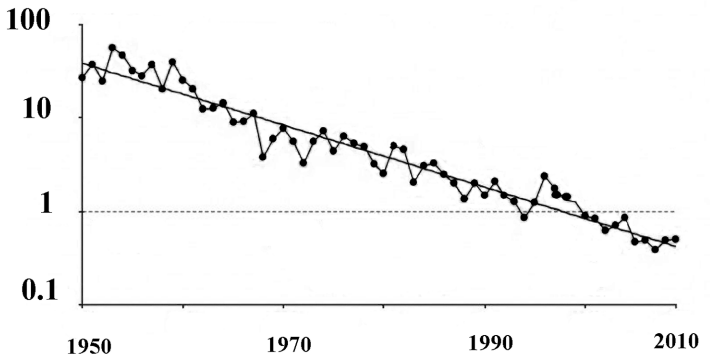

Figure 1: Adapted from Bernstein, 2010. The inverse Moore's Law for pharmaceuticals. The number of small molecule and biologic USFDA approvals per inflation-adjusted $ billion in research investment, 1950-2010. The apparent log-linear 'decline in research productivity' represents the failure of complex physiological processes to respond to simple interventions. Western medicine, as defined in the latter half of the 20th Century, has hit a brick wall, a catastrophic regime of exponential cost increase.

We begin with a review of a canonical formal approach to complicated biological and other dynamics.

2 Symbolic dynamics of complex physiological development

Symbolic dynamics is a 'coarse-grained' perspective on complicated systems that discretizes their time trajectories in terms of dynamically accessible regions so that it is possible to do statistical mechanics on symbol sequences (e.g., McCauley, 1993, Ch. 8) that can be said to constitute an 'alphabet'. Within that 'alphabet', certain 'statements' are highly probable, and others far less so.

The simple (ideal) oscillating population process described by the equations $dX/dt = \omega Y, dY/dt = -\omega X$ has the solution $X(t) = \sin(\omega t), Y(t) = \cos(\omega t)$ so that $X(t)^2 + Y(t)^2 \equiv 1$, and

*Box 47, NYSPI, 1051 Riverside Drive, NY, NY, 10032. 212-749-5904 x14. Wallace@nyspi.columbia.edu

the system traces out a circular trajectory in time. Divide the $X - Y$ plane into two components, the simplest possible coarse graining, calling the halfplane to the left of the vertical Y axis A and that to the right B. This system, over units of the period $1/(2\pi\omega)$, traces out a stream of A's and B's having a very precise grammar and syntax: ABABABAB...

Many other such statements might be conceivable, e.g., AAAAAA..., BBBBB..., AAABAAAB..., ABAABAAAB...,

and so on, but, of the infinite number of possibilities, only one is actually observed, is 'grammatical'.

More complex dynamical models, incorporating diffusional drift around deterministic solutions, or elaborate structures of complicated stochastic differential equations having various domains of attraction – different sets of 'grammars' – can be described by analogous means (e.g., Beck and Schlogl, 1995, Ch. 3).

Rather than taking symbolic dynamics as a simplification of more exact analytic or stochastic approaches, it is possible to comprehensively generalize the technique itself. Complicated cellular or other physiological processes may not have identifiable sets of stochastic differential equations like noisy, nonlinear mechanical clocks, but, under appropriate coarse-graining, they may still have recognizable grammar and syntax over the long-term. Proper coarse-graining may, however, often be the hard scientific kernel of the problem.

The fundamental assumption for complicated biological developmental phenomena like the onset of infection or the failure of essential regulatory processes is that developmental trajectories can be classified into two groups, a very large set that has essentially zero probability, and a much smaller 'grammatical' set. For the grammatical/syntactical set, the underlying argument is that, given a set of developmental trajectories of length n, the number of grammatical ones, $N(n)$, follows a limit law of the form

$$H = \lim_{n\to\infty} \frac{\log[N(n)]}{n} \tag{1}$$

such that H both exists and is independent of path. If convergence occurs for some finite n_H, then the process is said to be of order n_H. This is a critical foundation of, and limitation on, the modeling strategy adopted here, and constrains its possible realm of applicability. It is, however, fairly general in that it is independent of the serial correlations along reaction pathways.

H is seen to represent the Shannon uncertainty of a classic information source (e.g., Ash, 1990; Cover and Thomas, 2006; Khinchin, 1957).

The basic argument is shown in figure 2, where an initial developmental configuration, $\mathbf{S}_0$, can either converge on a normal state $\mathbf{S}_{norm}$ via the set of high probability reaction paths to the left of the filled triangle, or it can converge to a thermodynamically competitive pathological state $\mathbf{S}_{path}$ to the right.

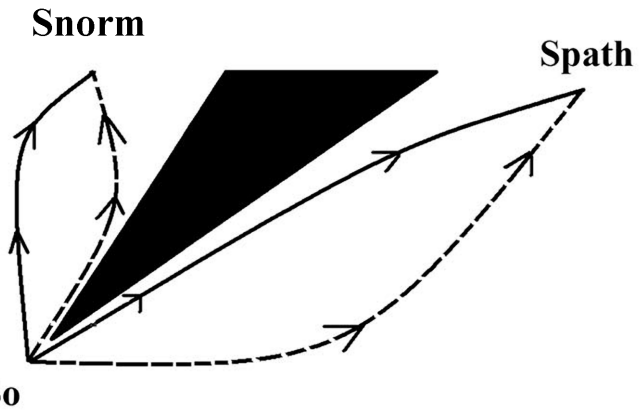

Figure 2: An initial physiological configuration $\mathbf{S}_0$ can either develop to a normal final configuration $\mathbf{S}_{norm}$ via the set of high probability reaction paths to the left of the filled triangle, or it can converge to a thermodynamically competitive pathological state $\mathbf{S}_{path}$ to the right.

We are, through coarse-graining and symbolic dynamics, assigning classic information sources to the two sets of thermodynamically competitive 'grammatical' pathways. The essential question is how, in general terms, an embedding physiological regulatory structure can act in such a circumstance to change the probabilities of convergence on $\mathbf{S}_{norm}$ or $\mathbf{S}_{path}$.

The mechanism implied by figure 2 has, in fact, been observed across much of molecular biology and been a subject of study for decades: Molecular systems may equilibrate between thermodynamically equivalent conformations until one is 'chosen', in a sense, by some external signal. Many examples can be found over the last 70 years, as described in the comprehensive review by James and Tawfik (2003).

More explicitly, Wallace (2011) has applied an 'information catalysis' model to biological logic gates whose activation or inhibition is triggered by selective binding by an intrinsically disordered protein, and this will serve as the basis for the approach taken here.

3 The dual information source of a cognitive regulatory process

The first step in answering the question of how pathways in figure 2 are 'chosen' lies in describing the activity of a large class of regulatory activity in terms of another information source. Atlan and Cohen (1998), in the context of a study of the immune system, argue that the essence of cognition is the comparison of a perceived signal with an internal, learned picture of the world, and then choice of a single response from a large repertoire of possible responses. Such choice inherently involves information and information transmission since it al-

ways generates a reduction in uncertainty. Structures that process information are constrained by the asymptotic limit theorems of information theory, in the same sense that sums of stochastic variables are constrained by the Central Limit Theorem, allowing the construction of powerful statistical tools useful for data analysis.

More formally, a pattern of incoming input $\mathbf{S}_i$ describing the status of the physiological system of interest – starting with the initial state $\mathbf{S}_0$ – is mixed in a systematic algorithmic manner with a pattern of otherwise unspecified 'ongoing activity', including cellular, epigenetic and environmental signals, $\mathbf{W}_i$, to create a path of combined signals $x = (a_0, a_1, ..., a_n, ...)$. Each a_k thus represents some functional composition of internal and external factors, and is expressed in terms of the intermediate states as

$$\mathbf{S}_{i+1} = f([\mathbf{S}_i, \mathbf{W}_i]) = f(a_i) \tag{2}$$

for some unspecified function f. The a_i are seen to be very complicated composite objects, in this treatment, that we may choose to coarse-grain so as to obtain an appropriate 'alphabet'.

In a simple spinglass-like model, $\mathbf{S}$ would be a vector, $\mathbf{W}$ a matrix, and f would be a function of their product at 'time' i.

The path x is fed into a highly nonlinear decision oscillator, h, a 'sudden threshold machine' pattern recognition structure, in a sense, that generates an output $h(x)$ that is an element of one of two disjoint sets B_0 and B_1 of possible system responses. Let us define the sets B_k as

$$B_0 = \{b_0, ..., b_k\},$$

$$B_1 = \{b_{k+1}, ..., b_m\}.$$

It is possible to assume an elaborate graded response, in precisely the sense studied by Pufall et al. (2005), supposing that if $h(x) \in B_0$, the pattern is not recognized, and if $h(x) \in B_1$, the pattern has been recognized, and some action $b_j, k+1 \leq j \leq m$ takes place. Typically, for the example of figure 2, the set B_1 would represent the final state of the developing system.

The principal objects of formal interest are paths x triggering pattern recognition-and-response. That is, given a fixed initial state $a_0 = [\mathbf{S}_0, \mathbf{W}_0]$, examine all possible subsequent paths x beginning with a_0 and leading to the event $h(x) \in B_1$. Thus $h(a_0, ..., a_j) \in B_0$ for all $0 < j < m$, but $h(a_0, ..., a_m) \in B_1$. B_1 is thus the set of final possible states, $\{\mathbf{S}_{norm}\} \cup \{\mathbf{S}_{path}\}$ from figure 2 that includes both the normal and pathological conditions.

Again, for each positive integer n, let $N(n)$ be the number of high probability grammatical and syntactical paths of length n which begin with some particular a_0 and lead to the condition $h(x) \in B_1$. Call such paths 'meaningful', assuming, not unreasonably, that $N(n)$ will be considerably less than the number of all possible paths of length n leading from a_0 to the condition $h(x) \in B_1$.

While the combining algorithm, the form of the nonlinear oscillator, and the details of grammar and syntax, can all be unspecified in this model, the critical assumption that permits inference of the necessary conditions constrained by the asymptotic limit theorems of information theory is that, again, the finite limit

$$H = \lim_{n \to \infty} \frac{\log[N(n)]}{n}$$

both exists and is independent of the path x.

Call such a pattern recognition-and-response cognitive process *ergodic*. Not all cognitive processes are likely to be ergodic in this sense, implying that H, if it indeed exists at all, is path dependent, although extension to nearly ergodic processes seems possible (e.g., Wallace and Fullilove, 2008).

Invoking the spirit of the Shannon-McMillan Theorem, as choice involves an inherent reduction in uncertainty, it is then possible to define an adiabatically, piecewise stationary, ergodic (APSE) information source $\mathbf{X}$ associated with stochastic variates X_j having joint and conditional probabilities $P(a_0, ..., a_n)$ and $P(a_n | a_0, ..., a_{n-1})$ such that appropriate conditional and joint Shannon uncertainties satisfy the classic information theory relations (Cover and Thomas, 2006)

$$H = \lim_{n \to \infty} \frac{\log[N(n)]}{n} = \lim_{n \to \infty} H(X_n | X_0, ..., X_{n-1}) =$$

$$\lim_{n \to \infty} \frac{H(X_0, ..., X_n)}{n+1} \tag{3}$$

This information source is defined as *dual* to the underlying ergodic cognitive process.

Adiabatic means that the information source has been parameterized according to some scheme, and that, over a certain range, along a particular piece of parameter trajectory, the source remains as close to stationary and ergodic as needed for information theory's central theorems to apply. *Stationary* means that the system's probabilities do not change in time, and *ergodic*, roughly, that the cross sectional means approximate long-time averages. Between pieces it is necessary to invoke various kinds of phase transition formalisms, as described more fully in e.g., Wallace (2005).

4 Information catalysis

In the limit of large n, $H = \lim_{n\to\infty} \log[N(n)]/n$ becomes homologous to the free energy density of a physical system at the thermodynamic limit of infinite volume. More explicitly, the free energy density of a physical system having volume V and partition function $Z(\beta)$ derived from the system's Hamiltonian – the energy function – at inverse temperature β is (e.g., Landau and Lifshitz 2007)

$$F[K] = \lim_{V\to\infty} -\frac{1}{\beta}\frac{\log[Z(\beta,V)]}{V} \equiv$$

$$\lim_{V\to\infty} \frac{\log[\hat{Z}(\beta,V)]}{V},$$

(4)

with $\hat{Z} = Z^{-1/\beta}$. The latter expression is formally similar to the first part of equation (3), a circumstance having deep implications: Feynman (2000) describes in great detail how information and free energy have an inherent duality. Feynman, in fact, defines information precisely as the free energy needed to erase a message. The argument is surprisingly direct (e.g., Bennett, 1988), and for very simple systems it is easy to design a small (idealized) machine that turns the information within a message directly into usable work – free energy. Information is a form of free energy and the construction and transmission of information within living things consumes metabolic free energy, with inevitable losses via the second law of thermodynamics.

Information catalysis, in the circumstance of figure 2, arises most simply via the 'information theory chain rule' (Cover and Thomas, 2006). Given X as the information source representing the reaction paths of figure 2, and Y, an information source dual to the sophisticated biochemical cognition of the regulating system, one can define jointly typical paths $z_i = (x_i, y_i)$ having the joint information source uncertainty $H(X,Y)$ satisfying

$$H(X,Y) = H(X) + H(Y|X) \leq H(X) + H(Y).$$

(5)

Of necessity, then,

$$H(X,Y) < H(X) + H(Y)$$

(6)

if $H(Y|X) < H(Y)$.

These relations imply that, by means of the identification of information as a form of free energy, at the expense of adding the considerable energy burden of the regulatory apparatus, represented by its dual information source Y, it becomes possible to canalize the reaction paths of figure 2, so as to make one set of pathways beginning with $\mathbf{S}_0$ far more probable than another.

That is, by raising the entire reaction free energy landscape corresponding to $H(X)$ by the amount $H(Y)$ it becomes possible to deepen the energy channel leading from $\mathbf{S}_0$ to the desired outcome, either $\mathbf{S}_{norm}$ or $\mathbf{S}_{path}$. Complicated internal reaction mechanisms have been subsumed by the Shannon-McMillan Theorem, in the same sense that the Central Limit Theorem subsumes the behavior of long sums of stochastic variates into the Normal distribution.

Within an organism, however, there will be an ensemble of possible developmental states and pathways, driven by available metabolic free energy, so that, taking $< .. >$ as representing an average,

$$[< H(X,Y) >] < [< H(X) > + < H(Y) >].$$

(7)

Typically, letting M represent the intensity of available metabolic free energy, a rate index, one expects

$$< H > \approx \frac{\int H \exp[-H/\kappa M] dH}{\int \exp[-H/\kappa M] dH} \approx \kappa M,$$

(8)

where κ, an inverse energy rate scaling constant, may be quite small indeed, a consequence of entropic translation losses between metabolic free energy and the expression of information. Thus equation (8) converges as indicated.

The resulting relation,

$$M_{X,Y} < M_X + M_Y,$$

(9)

suggests an explicit free energy mechanism for developmental canalization: at the expense of maintaining the complex regulatory process Y it becomes possible to canalize the developmental pathways of the information source X via a kind of information catalysis.

That is, quite counterintuitively, entropic loss – small κ – can be a powerful tool for triggering complex biological logic gates like figure 2, in much the same sense that Tompa and Csermely (2004) propose that entropy transfer can be used by generalized chaperones to trigger proper conformation in pathologically folded protein complexes.

We now build a sequence of statistical models based on these foundations.

5 Nonequilibrium 'equilibria'

The tool for this is a version of Onsager's phenomenological nonequilibrium thermodynamics. Redefine, now, the metabolic free energy intensity measure $M_{X,Y_1,...,Y_m}$ as F, where X represents the developmental system of interest and the Y_i are regulatory or environmental signals operating at different scales and levels of organization.

Assuming F is parameterized by some set of appropriate variates $\mathbf{Q} = [Q_1, ..., Q_n]$, it becomes possible to write an 'entropy' in standard form as

$$S \equiv F - \sum_k Q_k \partial F / \partial Q_k. \tag{10}$$

The phenomenological Onsager equation becomes

$$dQ_j/dt = \sum_i L_{i,j} \partial S / \partial Q_i, \tag{11}$$

where the $L_{i,j}$ are empirical constants, and the partial derivatives represent 'thermodynamic forces' driven by gradients in the entropy. It is important to note, however, that, for this system, one cannot have 'reciprocity relations' of the form $L_{i,j} = L_{j,i}$ since the underlying information sources, of which M is an environmental index, are not micro-reversible. For example, in English the short string ' eht ' does not have the same probability as the equally short string ' the '.

Equation (11) has the standard generalization as a stochastic differential equation

$$dQ_t^j = L_j(t, Q^1 ... Q^n)dt + \sum_j \sigma_j(t, Q^1, ..., Q^n) dB_t^i, \tag{12}$$

where the dB_t^i represent different kinds of 'noise' whose characteristics are usually expressed in terms of their quadratic variation. See, e.g., Zhu et al. (2007) for an example, and any standard work on stochastic differential equations or Brownian motion for a tutorial (e.g., Protter, 1990).

Several points emerge:

1. The different configurations possible to this 'coevolutionary' system are found by setting the system of equation (12) to zero, and solving for stationary points, since the noise terms preclude unstable equilibria.

2. The system may, however, converge to limit cycle or pseudorandom 'strange attractor' behaviors in which it seems to chase its tail endlessly within a limited venue – a kind of 'Red Queen' pathology.

3. What is converged to, in both cases, is not a simple state or limit cycle of states, but rather an equivalence class, or set of them, of highly dynamic information sources coupled by mutual interaction through crosstalk that have simply been parameterized by the free energy intensity measure $F = M_{X,Y_1,...}$. 'Stability' in this structure represents particular patterns of ongoing dynamics rather than some identifiable static configuration.

Most importantly, as Champagnat et al. (2006) note, shifts between the quasi-equilibria of a coevolutionary system like this one can be addressed by the large deviations formalism. They find that the issue of dynamics drifting away from trajectories predicted by the canonical equation can be investigated by considering the asymptotic of the probability of 'rare events' for the sample paths of the diffusion.

By 'rare events' they mean diffusion paths drifting far away from the direct solutions of the canonical equation. The probability of such rare events is governed by a large deviation principle: when a critical parameter (designated ϵ) goes to zero, the probability that the sample path of the diffusion is close to a given rare path ϕ decreases exponentially to 0 with rate $\mathcal{I}(\phi)$, where the 'rate function' $\mathcal{I}$ can be expressed in terms of the parameters of the diffusion. This result, in their view, can be used to study long-time behavior of the diffusion process when there are multiple attractive singularities. Under proper conditions the most likely path followed by the diffusion when exiting a basin of attraction is the one minimizing the rate function $\mathcal{I}$ over all the appropriate trajectories. The time needed to exit the basin is of the order $\exp(V/\epsilon)$ where V is a quasi-potential representing the minimum of the rate function $\mathcal{I}$ over all possible trajectories.

An essential fact of large deviations theory is that the rate function $\mathcal{I}$ which Champagnat et al. invoke can be expressed as a kind of entropy, that is, having the canonical form

$$\mathcal{I} = -\sum_j P_j \log(P_j)$$

(13)

for some probability distribution. This result goes under a number of names; Sanov's Theorem, Cramer's Theorem, the Gartner-Ellis Theorem, the Shannon-McMillan Theorem, and so forth (Dembo and Zeitouni, 1998).

These considerations lead very much in the direction of equation (12), but now seen as subject to internally-driven large deviations *that are themselves described as information sources*, providing $Q = f(\mathcal{I})$-parameters that can trigger punctuated shifts between quasi-stable modes. Thus both external signals, characterized by the information source Z, and internal 'dynamic ruminations', characterized by the information source $\mathcal{I}$, can provide Q-parameters that serve to drive the system to different quasi-equilibrium states – pathological or benign – in a highly punctuated manner, if they are of sufficient magnitude.

In particular, $\mathcal{I}$ is not likely to represent a simple 'magic bullet' intervention, but rather may involve a complex intervention strategy that must operate across a variety of scales and levels of organization.

6 Discussion and conclusions

Complex multi-level regulatory behaviors, and their failures as affected by environmental interactions or internal dynamics, have been modeled in terms of a nested set of information sources that are constrained by the asymptotic limit theorems of information theory, and this may allow construction of regression- or Onsager- model-like statistical tools useful for scientific inference, focusing on the behaviors of the system rather than on a detailed description of its mechanical state under all circumstances and at all times. The analogy is to characterize the behavior of a computer in terms of its program, rather than attempting provide a full cross-sectional statement of the condition of each logic gate at each clock cycle.

The composite regulatory and/or embedding 'logic gates' affecting figure 2 are likely to be quite different from 'simple' computer models, having extraordinarily subtle properties: evolution is not restricted to binary mathematics (AND, OR, XOR, etc.).

These considerations add considerable weight to an emerging perspective that sees a fundamental defining characteristic of the living state as the operation of chemical or other cognitive processes at virtually all scales and levels of organization (e.g., Wallace, 2011; Wallace and Wallace, 2010; Atlan and Cohen, 1998; Cohen, 2000; Wallace, 2005; Wallace and Fullilove, 2008).

From that viewpoint, the solution to the conundrum of figure 1 is to reconfigure interventions so as to encapsulate more than a single scale or level of organization. That is, it has now become necessary for the pharmaceutical industry – and its medical associates – to move beyond small molecule design to the principled construction of more comprehensive multifactorial or multiscale interventions designed to affect the interaction of complementary biochemical and information source networks, driving them from pathological to benign conformations, using 'large deviations' in the sense of equation (13).

At the individual level this would appear to require seeking synergistic total strategies that act across levels of organization, rather than applying a sequence of scale-limited magic bullets, a difficult tectonic shift in scientific perspective, research, and practice not likely to prove popular with those embedded in current funding streams.

At the population level, where public policy can be most effective, the increasing expense of individual level interventions – even if the rate of decline of figure 1 can be mitigated as we suggest – would seem to imply the necessity of again recognizing what has been known for the last two hundred years, that patterns of health and illness are determined by living and working conditions and the power relations between groups (e.g., Kleinman, Das and Lock, 1994; Wallace and Fullilove, 2008; Wallace et al., 2009; Wallace and Wallace, 2010).

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