Toward a Nonlinear Network Theory of Complex Disease

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1.1. Introduction

It is becoming increasingly recognized that many common diseases, such as cancer, asthma and hypertension, are best described as being "complex". These diseases are characterized by multi-factorial etiologies, widely varying prognoses, and frequently unclear therapeutic options. Recent history lends equivocal support to the notion that many complex diseases will be cured in the foreseeable future. Indeed, some opine that the cell and molecular biology revolution of the past two decades has not delivered on its initial promise (Macklem 2004). One possible reality of complex diseases is thus that they are just complex. That is, they involve innumerable players, assembled haphazardly by millions of years of evolution, whose interactions somehow become unbalanced. If true, we must resign ourselves to a future in which complex pathophysiology is elucidated gradually through the painstaking excavation of disparate facts from a vast biological landscape. This is a sobering thought because it means that cures will be approached asymptotically. Nevertheless, research into complex diseases tends to be sustained by the more optimistic outlook that significant advances will come in quantum leaps. The attraction of this outlook derives in large part from the fact that it keeps the hope of imminent cure alive. It also promises the intellectual satisfaction of progress in the form of novel insights rather than the mere accumulation and management of vast quantities of data.

It is in the spirit of the optimistic outlook that researchers are turning to the view of biological systems as dynamic networks (Kitano 2002; Aldana and Cluzel 2003; Bray 2003). Now the challenge is to figure out how to take the "dynamic network" concept from the level of appealing notion to genuine advance. One avenue of approach is based on the notion that living biological systems exhibit emergent behavior that depends on certain general organizational principles, but which is independent of the system itself beyond a certain level of detail. Uncovering these general principles would then constitute a significant step forward, with major implications for the understanding of complex diseases.

1.2 Biological Networks

1.2.1 "Small World" Networks and Power Laws

It seems clear that biological behavior, and indeed life itself, represent emergent phenomena arising within dynamic networks. A general question that arises concerns the topology of such a network, how the nodes are connected to each other Do biological networks share some common topological feature, or are they structured purely according to their specific functions which may or may not be related?

An answer to this question is suggested by the substantial amount of recent research showing that spontaneously arising networks tend to obey the "small world" principle in which every element in the network can be reached from every other element by traversing, on average, only a small number of links, even when the total number of elements is huge (Barabasi and Albert 1999). This is achieved by having the number of links impinging on an arbitrarily chosen node follow a power-law probability distribution. In other words, a small number of nodes (called hubs) are highly connected, while most nodes connect directly to only a very few other nodes. This topology has been demonstrated in networks arising all over the natural world, including in biological systems such as protein networks (Ravasz, Somera et al. 2002).

1.2.2 Homeostasis and Chronic Disease

Most minor perturbations that a healthy individual experiences in daily life, such as receiving a bruise or catching a cold, are transient experiences against which the body is able to mount a response that eventually returns things back to normal. By contrast, a general characteristic of complex diseases, apart from their resistance to elucidation, is that they tend to be chronic (e.g. asthma, hypertension); the homeostatic balance of health seems to become disrupted in a way that is resistant to treatment. In light of the foregoing, this suggests that minor ailments respresent a small shift away from dynamic equilibrium, while in chronic disease a biological network is placed in a permanently altered state. We identify three distinct mechanisms by which the state of a dynamic network can be permanently altered.

1. Altered network structure: The most obvious way of changing network behavior is to damage it, either by loss of nodes or breakage of links. The causative agent could be either some external influence or simply degeneration from within. Treatment of a damaged network is presumably a matter of locating and repairing the damage.

2. Persistent insult: A living system requires input from the environment, either continuously (e.g. oxygen) or periodically (e.g. food), but is also subject to noxious inputs. A noxious input applied briefly (e.g. a glass of whisky) may upset the homeostatic balance transiently, but this balance is expected to return to normal in time. By contrast, if the noxious input is applied persistently, an ongoing disruption of homeostasis is expected. The progressive granulomatous lesions caused by particles of silica in the lung may be such an example (Davis 2002). Treatment of disease caused by a persistent insult is obviously a matter of finding and removing the insult.

3. Entrapment in a local energy minimum: The third way of altering network behavior is the most subtle, and arises because dynamic networks may have more than one dynamically stable state defined by the pattern of activities of its nodes and links. Transition between different stable states may be elicited by suitable external stimuli. Furthermore, once such a state transition has been achieved, removal of the stimulus will not necessarily reverse the situation. Chronic disease might then be the result of an environmental insult that moves the network from its state of health to one of permanently pathology. This would occur with no change in network structure, so there would be nothing to repair. Furthermore, searching for the initiating event, which could be long gone at the time of diagnosis, would also be futile. The enigmatic nature of a pathology of this kind would make its correction especially problematic.

1.3 A Network Model of Complex Disease

1.3.1 The nature of nodal interactions

As we noted above, evidence indicates that biological networks tend to conform to the small-world topology. However, this does not tell us how information or energy flows along these pathways, which is what determines the way the network actually functions and which has thus far received relatively limited attention with respect to biological systems (Bar-Yam and Epstein 2004). The simplest possibility is that each node dispenses information to its recipient nodes according to first-order linear kinetics. However, this would make the network nothing more than a multi-compartment linear system. The overall behavior of a system of n such compartments is described by an nth-order linear differential equation, which predicts behavior that always converges to only a single steady-state solution – hardly the basis for something as interesting and varied as biological behavior.

This suggests that nonlinearities must feature in some important way in the inter-nodal connection dynamics of a biological network. Indeed, the seminal importance of dynamic nonlinearities is a well-accepted notion amongst theoretical biologists, being a key feature of, for example, cellular automata (Wolfram 2002). Nevertheless, simply saying that nonlinearities must be present is relatively unhelpful, given the limitless possibilities this allows for. What is needed is some insight into the general nature of these nonlinearities. One possibility is suggested by a well-studied construct known as the artificial neural network (ANN).

1.3.2 The Essence of Artificial Neural Networks

The study of ANN's is now a huge field with many applications (Haykin 1995). The essence of the ANN, however, is straightforward; it is a network in which each node is

an artificial neuron receiving a number of inputs and producing an output. The relationship between the sum of the inputs to and the output from a neuron is a saturation-type nonlinearity, which means essentially that the neuron does not "fire" (produce an output) until its inputs sum to a certain level. Once this level is achieved and the neuron fires, further increases in input have relatively little affect on the level of the output. The output of the neuron becomes an input to a number of other neurons after having first been multiplied by a weighting factor associated with the corresponding link. The precise shape of the saturation nonlinearity associated with each artificial neuron does not seem to be critical to the overall function of an ANN. What is important is that the neuron does not fire when the inputs are low, it does fire when the inputs are high, and it makes a fairly steep transition in between. The many interesting properties of ANN's stem from their various topologies and the values of the synaptic weights between individual neurons.

Probably the most widely studied type of ANN is the multilayer perceptron, which can be trained to solve the general pattern recognition problem because it can define an arbitrarily complex segmentation of n-dimensional feature space (Haykin 1995). The biological significance of the multilayer perceptron was not lost on Bray (Bray 2003), who noted it shares a striking formal similarity with the signaling cascade between the surface receptors and nucleus of a cell. This suggests the intriguing possibility that nuclear transcription of a given protein is induced not by activation of a single receptor, but rather by a pattern of activation distributed across multiple receptor types. Nevertheless, the multilayer perceptron is not well suited to the modeling of dynamic processes because it does not involve cycling patterns of activity.

We therefore now turn our attention to "re-entrant" types of ANN in which information from one neuron is fed back, possibly via a series of links, to neurons that it receives input from. The most well-studied re-entrant ANN is the Hopfield net (Hopfield 1984) in which every neuron is connected to every other neuron. The output of each neuron also goes from quiescent to full firing as soon as the inputs to that neuron sum to a certain critical level. Each neuron thus exists in one of two states, on or off. The Hopfield net is also symmetric; the synaptic strength of the link from node *i* to node *j* is the same as that from *j* to *i*. It can be shown that if a Hopfield net is given some particular configuration of neuron states, and each neuron is then allowed to continually process its inputs and recalculate it output, the neuron states will converge toward a steady-state pattern. Furthermore, a given Hopfield net can have a number of different steady-state patterns, and the pattern to which it converges depends is the one which is closest to the initial set of states. This property allows the Hopfield net to perform associative memory functions, such as letter recognition, from which stems it tremendous practical advantages (Haykin 1995).

1.3.3 Stability in Re-entrant Networks

If the synaptic strengths of the Hopfield net are allowed to be asymmetrical, the network does always converge toward a single stable state; a variety of other behaviors are also possible. For example, the network behavior may converge toward a repeating pattern of two or more states that it cycles between indefinitely. Alternatively, it may

not converge to any single dynamic pattern at all, but rather may move chaotically between different states. The particular pattern of behavior that a re-entrant network exhibits depends on its structure, that is, the network topology and the strengths of the synaptic connections. What is more significant for biology, however, is that the asymptotic dynamic behavior of a network can also depend on its initial conditions. In other words, exactly the same network can behave very differently depending on the pattern of nodal states it starts with.

This kind of behavior is illustrated by the following example of a 16-node asymmetric network. The network is given the power-law topology described above by having one of its nodes provide inputs to all 16 nodes, another two nodes provide inputs to 8 of the nodes, a further 4 nodes provide inputs to 4 nodes, and the remainder apply inputs to only two nodes. Furthermore, to give the network a biological flavor the nodal nonlinearities are described by the Michaelis-Menton equation. In other words, the links represent factors that either enhance or suppress the ability of substrate-ligand reactions (the nodes) to take place, as might be expected of a network of biochemical reactions in the body. The synaptic weights for the non-zero links are chosen randomly from a uniform distribution between –1 and 1. Thus, some of the links are excitatory and others inhibitory, including any feed back from a node to itself.

Associated with each node are two constants, V and C, corresponding to the maximum reaction rate and the concentration at half maximum rate, respectively, as required to define Michaelis-Menton reaction kinetics. The state of node i at time t, $x_i(t)$, is thus determined by the sum of the weighted inputs it receives from other nodes at time t-1 processed through the Michaelis-Menton equation, thus

$$x_i(t) = \frac{V_i \sum_j w_{ji} x_j(t-1)}{C_i + \sum_j w_{ji} x_j(t-1)} \qquad (1)$$

The value of V_i is equal set to 1 for all nodes, while the C_i are chosen randomly from a uniform distribution between 0 and 1. The network is initiated with the x_i also assigned random values between 0 and 1. The network is then repeatedly iterated by recalculating every x_i according to Eq. 1.

If this network is given different values for its synaptic weights, it will exhibit a variety of different types of asympototic behavior, from a regularly repeating pattern of one or more states to a sequence of states that seemed to continue chaotically without repeating any pattern. However, a given realization of this network can also converge toward different behavior patterns depending on its initial configuration, as demonstrated in Figs. 1 and 2. Figure 1 shows an example of two different initial configurations of the same network that lead to the same stable state. Figure 2 shows the result of starting the same network from yet another initial state, but this time it converges to a limit cycle that switches at alternate time steps between two fixed states.

1.3.4 Attractors and Entrapment

The above example, although highly contrived, demonstrates the potential for biological networks to operate around multiple stable states, each acting as an

"attractor" for network states that are nearby. Suppose one such state corresponds to "health" (i.e. the normal state). Small perturbations away from this state, such as might be induced by a modest environmental insult, would then be expected to resolve over time back toward the healthy state. (This might correspond to, say, exposure to an antigen typically produces an inflammatory reaction that flares up quickly and then resolves completely in time.)

However, as the initial state moves further away from the stable state to which it is attracted, there will suddenly come a point where a new stable state assumes the role of attractor. When this happens, spontaneous return to the original stable state will no longer be possible. The obvious biological analogy suggested by this scenario is that chronic disease may correspond to an aberrant dynamic stable state that just happens to be closest to whatever state the biological network is placed in following a sufficiently severe insult. It remains to be seen whether this entrapment mechanism is behind any chronic idiopathic lung diseases.

1.4 Conclusions

Complex diseases seem to exhibit characteristics reminiscent of a network that has been permanently shifted away from its normal state of dynamic equilibrium. Apart from the obvious causes of structural damage and ongoing insult, we note that this may happen to nonlinear networks when they become trapped in an alternate stable dynamic state. We have shown that a biologically motivated 16-node Hopfield-type network with small-world topology and Michaelis-Menton nodal functions is capable of exhibiting more than one dynamically stable state or limit cycle. This suggests that some chronic diseases may arise when just the right combination of environmental insults occur to push a healthy biological network into a pathological state from which spontaneous recovery is not possible.

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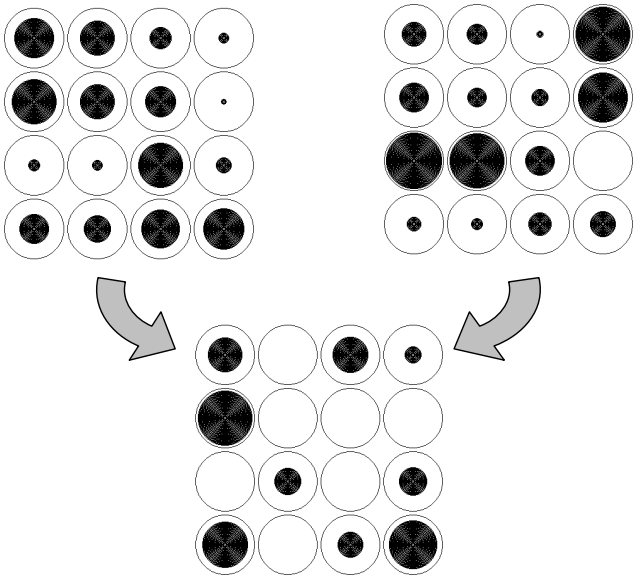

Figure 1: The two initial network states shown at top converged to the same stable state shown at bottom. The 16 nodes of the network can each take values from 0 to 1. The values of the nodes are indicated by the radii of the filled circles.

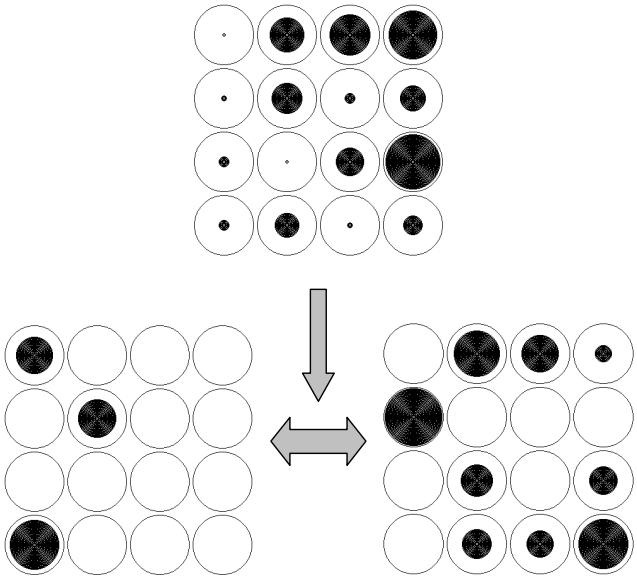

Figure 2: The initial state shown at the top converged to an oscillation between the two states shown at bottom.