The community of the self

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Good health, which reflects the harmonious integration of molecules, cells, tissues and organs, is dynamically stable: when displaced by disease, compensation and correction are common, even without medical care. Physiology and computational biology now suggest that healthy dynamic stability arises through the combination of specific feedback mechanisms and spontaneous properties of interconnected networks. Today's physicians are already testing to 'see if the network is right'; tomorrow's physicians may well use therapies to 'make the network right'.

Claude Bernard, the father of physiology, observed that diverse physiological mechanisms had a common purpose: those mechanisms maintain the interior of a biological entity stable in the face of stress. The brilliance of Bernard's insight cannot be denied. Whether a perturbation affects multiple organ systems globally or is targeted to a specific organelle, restorative mechanisms have been observed and proven to be functionally important to physiological stability. More recently, mathematicians and physicists studying network models of biological systems have suggested that stability need not be engineered, but rather can emerge as a property of the network and its interconnections. At all levels — from genes to the web of organ systems that make up an individual — it is the balance of autonomy and connectedness that sustains health. These two founts of stability have complementary roles in guarding the communities of cells that, in aggregate, is the organism itself.

Historical background

Early in the twentieth century, the Harvard physiologist Walter B. Cannon embraced and extended Bernard's concept to suggest that tight regulation of physiological parameters — what he termed "homeostasis" — was the result of restorative mechanisms that both sensed and corrected deviations from a normal state (Fig. 1). A medical doctor by training, Cannon went on to suggest that failed homeostatic mechanisms precipitated illness, and that the purpose of the clinician was to substitute for those mechanisms until control could be restored[1]. Cannon's imperative continues to drive the behaviour of physicians even today: the management of many common disease processes, such as diabetes mellitus, hypertension and hypercholesterolaemia, involves titration of drugs to normalize a measured value.

This substitution strategy seems most helpful when the disease process has a recognized mechanism and the drug(s) target the failure. More complex disease processes, particularly those that affect multiple mechanisms, have unpleasantly surprised well-intended doctors who have attempted to 'fix' parameters on their patients' behalf. For example, aggressive resuscitation to normalize blood pressure in penetrating trauma, infusion of calcium to correct the hypocalcaemia of sepsis, and (most recently) hormone therapies to replace menopausal deficiencies all may be harmful. Yet a talismanic belief in 'normal values' continues to permeate medical teaching and their restoration drives western medical practice.

A contemporary of Cannon's at Harvard University, Lawrence J. Henderson, embraced a more integrated perspective of biological regulation. His investigative focus was blood chemistry. Reasoning from physical and chemical principles of the time, it was Henderson who divined interrelationships from vast amounts of tabular data without benefit of computers. Henderson could predict numerically the behaviour of blood buffers provided that two values among the seven unknowns (total oxygen, total carbon dioxide, pO_2, pCO_2, pH, cell volume and anion concentration ratio across cell membranes) were presented. He developed nomograms that conveniently described those relationships and that were used subsequently by physicians for decades. Although students of biochemistry know him best for the eponymous Henderson–Hasselbach equation, his greater contribution may have been to stimulate physicians and scientists to evaluate physiological processes in the larger context of other biological systems. For Henderson, the organization of those systems and the mechanisms were not exclusive, but rather interdependent[2] (Fig. 1).

Systems theory and biology

Cannon and his disciples successfully pursued reductionist explanations of physiological stability in the face of perturbation. Pursuit, identification and description of mechanisms that restore and maintain measurable parameters ranging from vital signs (for example, temperature and blood pressure) to ion gradients remain a major research focus.

The notion that membership in a network could confer stability emerged from Ludwig von Bertalanffy' s description of general systems theory in the 1930s and Norbert Wiener's description of cybernetics in the 1940s. General systems theory focused in part on the notion of flow, postulating the existence and significance of flow equilibria. In contrast to Cannon's concept that mechanisms should yield homeostasis, general systems theory invited biologists to consider an alternative model of homeodynamics in which nonlinear, non-equilibrium processes could provide stability if not constancy. What Wiener did was blend systems theory and control theory (embedding in the title of his masterwork the notion that his ideas were equally applicable to animals and to machines) and demonstrating that communication and control were inseparable.

The fusion of systems theory with biology into systems biology required two types of developments: the theory had to be adapted to biological systems, and biological systems had to produce data suitable for evaluation and testing[3]. Both have depended heavily on computation. In the theoretical domain, Haken recognized that elements in a system

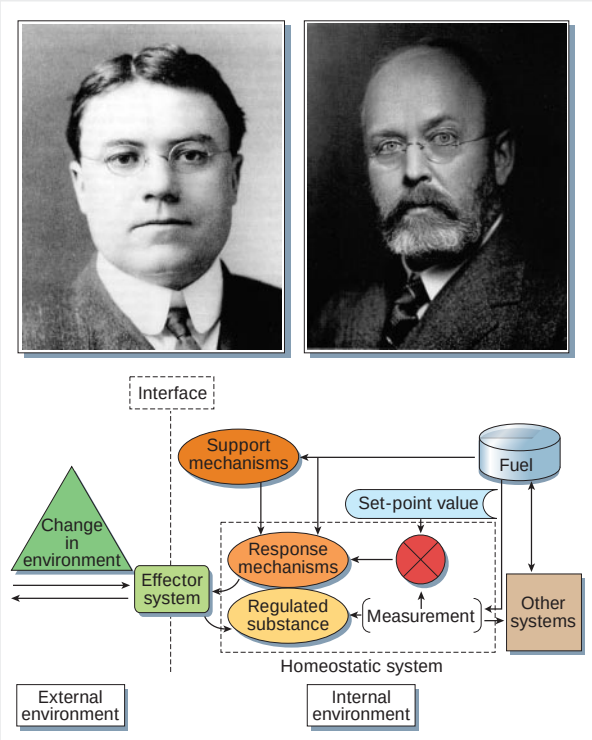


Figure 1 The concept of homeostasis. The top images are of Walter B. Cannon (left), who suggested that the presence of stable measurable parameters implied the presence of homeostatic systems, and his contemporary Lawrence J. Henderson (right), who provided a counterexample through his study of the buffering capacity of blood — the interactions among components were sufficient to confer stability without a separate regulating mechanism. The image below is a schematic of homeostasis. Changes in the environment are transduced to cause a change in the level of a regulated substance. This change is detected through measurement and comparison with a coded set-point value. Disparities between the measured value and the set-point value regulate a response mechanism that directly or indirectly influences effector systems at the exterior–interior interface. Homeostatic systems often require fuel, other support mechanisms and interact with other systems.

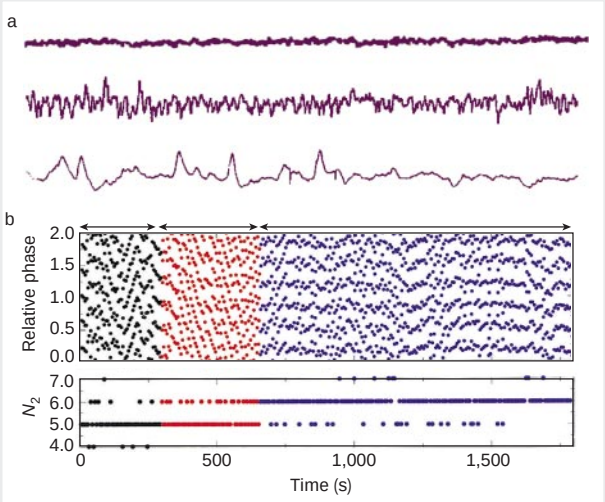


Figure 2 Interbeat variability in health, ageing and disease. **a**, Interbeat intervals obtained from electrocardiograms of three subjects (composite from refs 23, 35). Upper tracing, patient with severe congestive heart failure; middle tracing, healthy young subject; lower tracing, healthy aged subject. Compared to the healthy young subject, the aged subject and the patient with system failure have both lost variability, although the healthy aged subject retains more. **b**, A possible contributor to the healthy interbeat variability. This cardiorespiratory synchrogram illustrates the weak interaction between the cardiac and respiratory systems in a healthy young athlete at rest (image reproduced from ref. 36). The upper panel shows the phase relationship of each heartbeat within two respiratory cycles. The lower panel replots the data, showing that the coupling shifts from 5 heartbeats within 2 respiratory cycles ($N_2 = 5$) to 6 heartbeats within 2 respiratory cycles ($N_2 = 6$). Colours in the upper and lower panels show the transition (red) from 5:2 frequency locking (black) to 3:1 phase locking (blue). Studies by Goldberger and colleagues show that the seemingly 'regular' heartbeat of the young healthy heart is actually rather variable. Although some of that variability is accounted for by ventilation-dependent changes in the volume of blood returned to the heart, other sources of variation include rebalancing of autonomic tone. Both ageing and disease can increase the relative influence of sympathetic over parasympathetic components, leading to loss of variability. The synchrogram data suggest that uncoupling and recoupling are part of normal physiology. The acutely decoupled heart (such as the transplanted heart immediately following implantation) also has markedly diminished variability.

could cooperate spontaneously and developed rules about the factors that could facilitate and disrupt the appearance of coherent movement. The development of mathematical criteria that discriminate the spontaneous appearance of such cooperative behaviour led Haken to introduce the term 'synergetics'. More important than the term is the idea that in non-equilibrium systems (such as networks whose integrity depends on the availability of metabolic fuels), stable states may be far apart from one another, and moreover that the system can jump from one stable state to another.

Kauffman's computed simulation studies of toy systems configured as genetic networks showed that specifying the number and strength of connections among the elements of the network was sufficient to predict the canonical behaviours of the system (for example, the number of stable states). In aggregate, these experiments predicted that stability would arise in nearly every system in which elements that could assume a range of values were interconnected. In Kauffman's words, the stability need not be engineered — rather, interconnected networks provide "order for free"[4]. Collectively, the work of Haken and of Kauffman formed a foundation from which research on network dynamics and modern gene regulatory networks evolved. Studies of real genetic networks (through transcriptome analysis of cells in diverse states) tend to support the prediction: large subsets of genes are often strongly induced or repressed in an all-or-none response as cells move from one state to another.

Although science presently focuses on the simplest tractable system — individual cells — organization and regulation need to be defined at all levels of resolution if the source of stability is to be elucidated. Chauvet, studying mathematical models of formal biological systems, showed that nesting systems (biologically, this corresponds to the associations of cells into tissues, tissues into organs, and organs into the intact organism) could be spontaneous and would provide additional stability to the community of the self[5]. Kitano, who is one of the strongest proponents of modern systems biology, suggests that every system (irrespective of the level of resolution) be analysed with respect to the system's structure — its dynamics, its method of control and its method of design[6,7].

Coordinate responses to external stress

The responses to stress are critical to the maintenance of the community of the self. Such responses are triggered by violation of structural integrity (trauma), failure of other regulatory systems (for example, skin barriers) that permit microbial invasion or replication, and even endogenous threats such as cancer. There are at least two systems requirements. First, the multiple responses must coordinate, and second, they must be contained in space and time.

Box 1

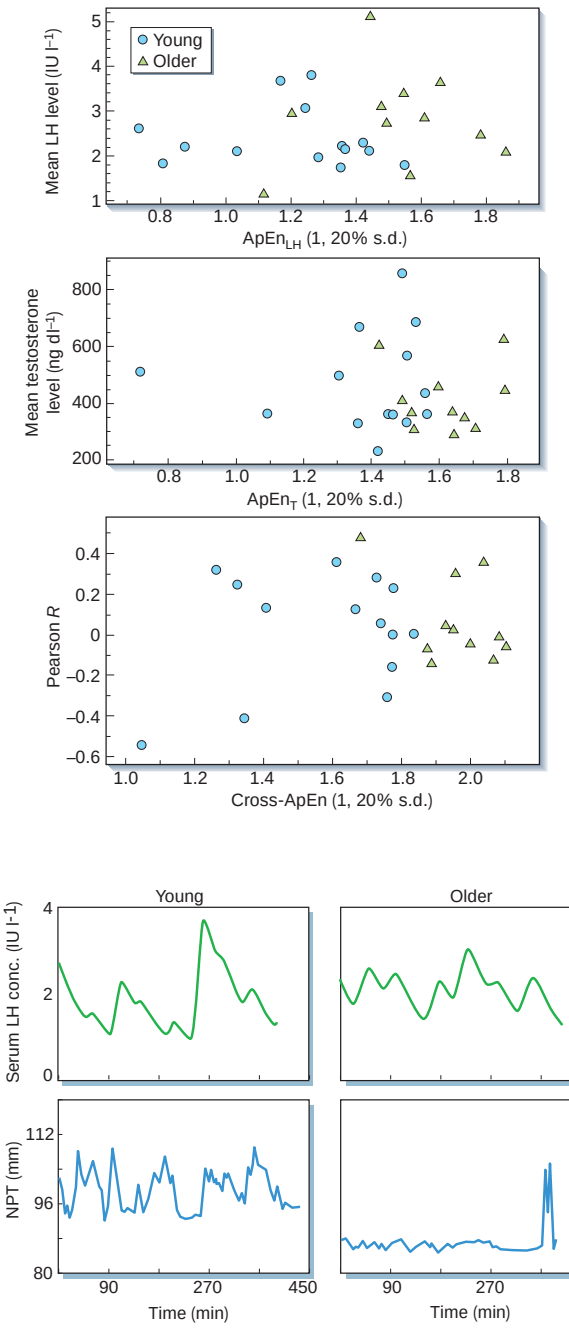
Tools to estimate coupling among systems

A task that challenges mathematical biologists who study the community of the self is the generation of unbiased estimates of coupling among different systems. One such estimate comes from a family of statistics called cross-ApEn. The parent family of statistics, approximate entropy or ApEn, measures the log likelihood that given each short pattern of a single data type, the next datum falls within an arbitrarily narrow range. Cross-ApEn measures the likelihood that given each short pattern of data in one data type, the next datum of another (putatively coupled) type falls within an arbitrarily narrow range. Two input parameters, *m* and *r*, are specified to compute ApEn and cross-ApEn. *m* represents the window (or vector) length of consecutive measurements; *r* represents the the tolerance for testing sub-pattern regularity. In order to maintain scale invariance, *r* is conventionally defined as a percentage of the between-sample variation (for example, 20% s.d.).

Pincus, who developed the ApEn and cross-ApEn statistics, has applied them to several clinical situations. For example, a study was performed to determine possible secretory irregularities with ageing in the luteinizing hormone/testosterone (LH–T) secretory axis (see upper three figure panels opposite, redrawn with permission from ref. 25). Serum concentrations were derived for the two hormones in 14 young (aged 21–34 years) and 11 older (aged 62–74 years) healthy men. For each subject, blood samples were obtained at frequent (2.5-min) intervals during a sleep period. When the age contrast in ApEn values for the luteinizing hormone and testosterone time series were considered singly (top two panels), mean (and standard deviation) concentrations of the two hormones were indistinguishable in the two age groups. Visual inspection of the scatterplots suggest that the secretion of luteinizing hormone and testosterone were more regular (lower ApEn) in the young subjects; however the separation between young and old subjects is incomplete. But when cross-ApEn was applied to the paired LH–T time series (lower panel), older subjects exhibited greater cross-ApEn values (1.961 ± 0.121) compared to younger subjects (1.574 ± 0.249; $P < 10^{-4}$), with nearly 100% sensitivity and specificity, indicating greater LH–T asynchrony in the older group. Moreover, no significant differences in LH–T linear correlation (Pearson *R*; $P > 0.6$) were found between the younger and older cohorts. Simple linear correlation does not detect the age-dependent differences in entwinement between secretion of luteinizing hormone and testosterone. Mechanistically, the results implicate LH–T network uncoupling as marking male reproductive ageing.

In a related study (see lower figure panels opposite, redrawn schematically from ref. 37, with permission), differences between younger and older males were studied based on several sex hormones and nocturnal penile tumescence (NPT) time series. The most vivid differences between the younger and older cohorts were that the paired LH–NPT dynamics were much more asynchronous in the older group. The timing between regulated hormonal (LH) input and target sexual response (NPT) output was significantly disrupted in the ageing male. This reinforces the point that successful therapeutic strategies probably need to be more integrative or network-oriented, rather than strictly local in structure.

Tools such as cross-ApEn facilitate pairwise comparison between the kind of time-series data that can be obtained, for example, from whole organs. Analysis of massively parallel data sets, such as data obtained from genomic studies, are hindered by high dimensionality:



the inter-relationships among ~10^4 data types are difficult to define from ~10^1 experiments (a value typical of current genomic experimental design). An important research goal would therefore seem to be the development of new tools that could extract possible inter-relationships among the data types and order the probability of those relationships objectively.

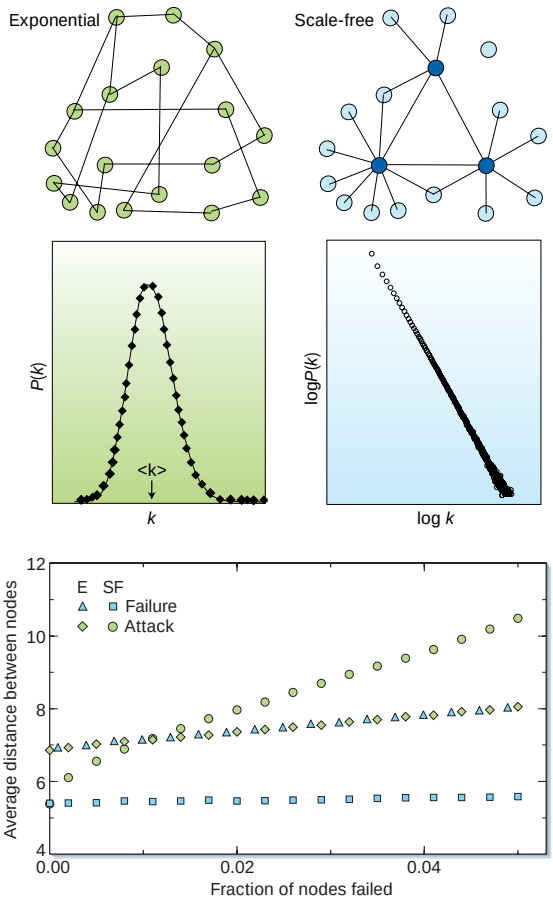
The main stress responses occur within cells and among cells. The principal intracellular response, originally called the heat-shock response, revises transcription and reassigns translation to produce several dozen gene products ('stress proteins') that collectively refocus metabolism on cleaning up denatured structures and fortifying the cell (at least temporarily) against subsequent insults. All cells produce the major heat-shock protein, Hsp72, an inducible chaperonin that sequesters and refolds damaged proteins (ref. 8; and see review in this issue by Koonin *et al.*, pages 218–223). The quantity and persistence of Hsp72 (and the other stress proteins) is roughly

Box 2
Network structure affects tolerance to node failure

Networks seem to promote physiological stability. Barabasi's group has compared two canonical types of network — exponential networks (also known as Erdös–Rényi networks) and scale-free networks (see upper four figure panels opposite, reproduced from ref. 38). The connectivities of these networks are different and are characterized by the probability $P(k)$ that a given node has k links. For an exponential network, $P(k)$ peaks strongly at $k = \langle k \rangle$ and decays exponentially for large k. In the scale-free network, most nodes have only a few links, but a few nodes, called hubs (dark blue), have a very large number of links. In this case $P(k)$ has no well-defined peak, and for large k it decays as a power-law, appearing as a straight line on a log–log plot.

Natural metabolic networks seem to be mostly of the scale-free type. This architecture carries specific implications concerning node dysfunction and consequent network failure. Provided that nodes fail randomly, interconnectedness is far better preserved in scale-free networks than in exponential networks. However, if a disease process attacks key nodes, the scale-free network is more susceptible to failure (see lower figure panel opposite, from ref. 39). Distances between nodes are, on average, smaller in scale-free (SF) networks than in exponential (E) networks that connect equal numbers of nodes (see distance at zero failure). As the fraction of failed nodes increases, the residual connectedness depends on the underlying architecture and whether the failure is random or occurs by attack on hubs.

Once the network has failed, restoration of function to key affected nodes is necessary, but the appropriate connections must be restored to ensure resurrection of function. In general, aged patients recover from serious illness much more slowly than do younger, similarly ill patients. It is possible that aged patients cannot search through the space of possible connections as efficiently as their younger counterparts. If so, then mathematical biologists may be able to help clinicians by exploring treatment strategies that guide the search as opposed to fixing the value of particular nodes.



proportional to the intensity and duration of the stress. Resolution of the stress is sufficient to attenuate the heat-shock response — no anti-heat-shock programme has been identified — and return the affected cell to its basal programmes of gene expression and metabolic function.

In contrast, inflammation is a cooperative response involving multiple cell types, orchestrated both locally and remotely, and affecting the host at multiple levels of resolution (from organism to gene expression). Extracellular responses depend on biological amplification, and so differ from the proportionate intracellular response. Following an ordinary laceration — such as a nick or cut caused by a razor — the dynamics of the response are familiar if not entirely predictable. Priority is given to controlling the associated haemorrhage as platelets are recruited to the injury site to form a plug, and the coagulation cascade is activated. Chemical signals are emitted from the wound, which alter both blood flow and vessel characteristics. The latter alterations also cause circulating cells such as polymorphonuclear leukocytes (PMNs) to stick to the endothelium lining the blood vessel wall and to traverse it. Once sequestered into the response site, PMNs inflict oxidative damage upon foreign entities and mononuclear phagocytic cells are recruited to clean up the debris. If the clean up is successful, the response fades away. Alternatively, if microbes become established and begin to proliferate, the inflammatory response widens to block the invaders through abscess formation.

Unlike the intracellular stress response, this multicellular inflammatory response involves multiple signal amplifications. Specific containment strategies are necessary to keep the processes in check. Local clotting does not become widespread because circulating anticoagulants (for example, protein C) are activated. Thrombus formation also invites activation of fibrinolysis. PMNs recruited to the site will die by apoptosis. Even if apoptosis is delayed, an internal switch in lipid biosynthesis (from leukotrienes and prostaglandins to lipoxins) caused by the interaction of PMNs with cells resident in the inflamed tissue reprogrammes those PMNs to promote resolution of inflammation[9]. The mononuclear cells and T-helper lymphocytes that initially secrete pro-inflammatory cytokine molecules shift synthetic programmes to favour anti-inflammatory cytokines. In isolation, these containment strategies also seem to fit reductionist models. The strategies agree perfectly with Cannon's construct of homeostasis, and the medical response to failure of homeostasis directly supports them: if the patient is still bleeding, administer procoagulants, and if the patient is clotting excessively, prescribe blood thinners.

However, the processes are not isolated. In ordinary parallel operation, the containment aspects of the intracellular and multicellular responses become decidedly nonlinear. This manifests clinically as context dependence of the response. Matzinger has suggested and demonstrated that the immune system does not merely distinguish between self and non-self; rather, it responds to new epitopes only when there is a concurrent signal indicating that the organism is endangered[10]. The consequence of inducing a heat-shock response in endothelial cells and in fibroblasts is similarly context dependent. When an inducer of the heat-shock response is applied to cells in their normal state, the cells become refractory to the adverse consequences of a subsequent inflammatory stimulus such as bacterial

lipopolysaccharide. In contrast, cells that have been recently stimulated with bacterial lipopolysaccharide and are then exposed to an inducer of the heat-shock response execute apoptosis[11]. In the language of algebra, the operators of the stress response, inflammation and heat shock do not commute (see review in this issue by Searls, pages 211–217). Thrombosis prior to an inflammatory response is typically self-limited. Thrombosis in the context of an inflammatory response can lead to regional or even disseminated intravascular coagulation, probably through failure of the containment mechanisms. Conventional negative feedback models of homeostasis do not readily explain such context dependencies.

Some have suggested that the context dependencies are merely artefacts of experimentation and of modern therapy, that is, maladaptive responses to the invention of the hollow needle, intravenous fluids, antibiotics and other paraphernalia of intensive care. Given the recent discovery of hardwired safety mechanisms, this seems unlikely. For example, Tracey and colleagues have recently identified a vagally mediated circuit through which the brain can directly shut down the production of inflammatory mediators by the largest population of fixed mononuclear cells in the human body[12,13]. Such safety mechanisms suggest that the context-dependent nonlinear interactions are necessary to the maintenance of the community of the self. The nonlinearities may eventually translate into therapeutic strategies. Weiss and colleagues have shown that viral transfer of the gene coding for Hsp70 into the lungs of rats markedly attenuates the pulmonary component of widespread inflammation initiated by bacterial peritonitis[14,15].

Multiple organ dysfunction syndrome

Safety mechanisms do sometimes fail. Until recently, the disruption of the community of the self following such failures precipitated death. Modern critical care, capable of supporting or even temporarily replacing the physiological function of vital organs, spawned a new disease, the multiple organ dysfunction syndrome (MODS). MODS is characterized by unbridled inflammation, remote in space and in time from the inciting event. Typically, an infection that seems to have been promptly identified and appropriately treated nevertheless causes a body-wide inflammatory response, leading to serial failure of the respiratory system, digestive system and renal system to perform their vital functions. The mortality of three-organ dysfunction is 60–80%, and MODS remains a leading cause of death in intensive care units. It now seems possible that MODS is the manifestation of widespread network failure[16–19].

Workers observed that during the descent into MODS, physiological time signals (such as the beat-to-beat interval of the electrocardiogram) would lose the fine variability observed in healthy patients. Reasoning from Pincus's observation that greater regularity could indicate increased system isolation, Godin suggested that unbridled inflammation could cause uncoupling of organs from one another, thus precipitating MODS[18,19]. Godin went on to show that injection of bacterial endotoxin into human volunteers seemed to cause mild uncoupling that manifest as loss of variability in the electrocardiogram signal[20]. Goldstein and colleagues have observed similar uncoupling of autonomic regulation in patients descending into clinical septic shock, and recoupling during the recovery period[21]. Neither is the uncoupling phenomenon peculiar to sepsis — it is also observed in the context of severe brain injury[22].

Although such observations do not prove unequivocally that network disruption is the cause of MODS, the clinical imperative would seem to include restoration and protection of network integrity. Rebuilding a network is likely to be an orderly process; a common sequence of organ failure — lungs, then gut/liver, and finally kidneys — is precisely the opposite order in which those organs mature during fetal life. Because of this, it could well be counterproductive to adopt the usual therapeutic strategy of adjusting and clamping measured outcomes (such as blood pressure and pH) that serve as proxies of organ function simultaneously into their normal ranges.

Connectedness and mechanisms

It now seems that Cannon and Henderson were both correct. The community of the self appears to depend on classical homeostatic mechanisms as well as network integrity. An observed disruption of the stable state now raises a critical, if generic, issue: is it a specific mechanism or is it the connectedness among components that underlies the disruption? Mathematical biologists may help provide answers suggested by studies of physiological time signals in normal ageing (Fig. 2). Aged patients have stable, yet brittle, physiology. In addition to diminished reserves in nearly all systems, aged patients recover only slowly — or not at all — once physiological reserves are exceeded and medical intervention is necessary. It is not that aged patients have maladaptive responses to stress — rather their adaptive responses are inadequate. Goldberger and colleagues, reviewing fractal dynamics in physiology, note that many physiological time signals — from the heartbeat to gait — exhibit long-range correlation and rich multiscale dynamics. With age, such signals break down in two general ways, either exhibiting excessive order or uncorrelated randomness. These patterns of breakdown suggest that, for any physiological system, there is a range of connectedness that is optimal[23].

There exist several families of statistics that describe the regularity of time signals. One of them, approximate entropy (ApEn) serves as a useful example (Box 1). ApEn describes the likelihood that patterns recur in time signals[24] — decreases in ApEn correspond to decreases in pattern variability. The time signal of the heart (that is, the beat-to-beat intervals of the electrocardiogram) loses variability in normal ageing as it does in MODS. This loss of ApEn can be interpreted as isolation of the time signal source from the network. A derivative of ApEn called cross-ApEn describes the synchrony (coupling) that exists between pairs of time signals[25]. When coupling is tight, events in one signal cause predictable patterns in the other signal and cross-ApEn remains low. Tightly coupled time signals are common in classical homeostatic mechanisms owing to the link between signals and responses. An example of such linked signals is luteinizing hormone and testosterone in males. With ageing, the relationship between luteinizing hormone and testosterone becomes asynchronous; this manifests as an increased cross-ApEn value, and suggests that the tight link has begun to erode. Statistics such as ApEn and cross-ApEn may prove more generally useful to interrogate physiological time signals for evidence of mechanistic integrity and network integrity.

Although network integrity is important to health, it is not a strict proxy. Schäfer and colleagues, studying the weak interaction between the cardiac and respiratory systems in healthy athletes at rest, noted that the two systems uncouple and recouple every few minutes[26] (Fig. 2). The connection strengths between systems, and probably within systems, seem to be plastic. Kaneko's laboratory recently reported that even such plastic networks composed of chaotic units will self-organize into hierarchical structures[27]. Provided that the plasticity is limited, such uncoupling and recoupling may be part of healthy network physiology at many scales of resolution, from gene networks to organ systems. In this perspective, MODS may be less a problem of extended uncoupling and more a problem of failure to recouple (Box 2).

Such coupling relationships span multiple levels of resolution, an observation that demands bridging of molecular mechanisms and genetic data with physiological systems and function. Noble's wry vision of "genes as 'prisoners' that are trapped inside the successful physiological systems that express them" speaks to the ambiguity of causation in complex networks[28]. Although bench studies of network relationships provide important estimates of kinetics, their scope is necessarily narrow and confined typically to a single level. To address this limitation, projects such as the Human Physiome Project (http://www.physiome.org.nz/anatml/pages/index.html)

are undertaking development of tools and computer languages that capture representations of known pathways and convert them to common modelling code, thus facilitating merger and enabling a more complete visualization.

This approach has yielded substantial progress in modelling and understanding the human heart. Here, parallel research tracks in genetics, cell biology and organ physiology have been linked through Physiome Project tools to provide new insight into normal pathways of electrical conduction and the pathological events that are clinically manifested as life-threatening arrhythmias[29]. Finer-grained but more richly detailed simulations of intracellular events are being performed using the Virtual Cell modelling environment (http://www.nrcam.uchc.edu/vcell_development/vcell_dev.html), describing network-dependent phenomena such as calcium oscillations[30] and nuclear envelope breakdown.

As made apparent by Pincus, tighter coupling of independent signals with random components increases the stochastic behaviour of both. Tightening the coupling and increasing the stochastic components may have a physiological advantage. Collins and colleagues have explored the consequences of applied stochastic resonance, which arises from superposition of different types of noise (white, power-law and even coloured noise with long-range correlation) upon a low-amplitude signal. The noise serves to transiently amplify the signal above an otherwise unattained threshold. An exogenous noisy background thereby improves such diverse functions as tactile perception in diabetic neuropathy and perhaps even the effectiveness of life-supporting mechanical ventilation[31–34]. Perhaps more important, such noise appears endogenously in several physiological systems (see review in this issue by Rao and colleagues, pages 231–237).

Systems physiology: back to the future?

During the heyday of systems physiology — the middle third of the twentieth century — the inventory of many biological laboratories included larger animals, pressure transducers, flow probes and strip chart recorders. Relationships among data were distilled exclusively through inspection, and the analytic tool of the day (regression) concealed a bias for reductionist models that are now recognized to inadequately describe interconnected networks. The dawn of genomics (and, more generally, the promises of molecular medicine) tumbled systems physiology as a leading investigative approach. Yet clinicians continue to rely most heavily on systems physiology — such as bedside haemodynamics and respiratory dynamics — to promote the integrity of self, suggesting that a deeper understanding may yield new therapies.

Interest is now being rekindled in studies of systems physiology, especially those conducted in concert with genomic, transcriptomic, proteomic and metabolomic investigations. Digitized streams of physiological parameters create new analytic challenges that can be met only through partnerships among theorists, experimentalists and analysts. It is vital to create models that embed homeostatic mechanisms into larger networks that themselves confer robustness to perturbation and thereby protect the community of the self. But more important, and much harder, will be determining whether a particular model or class of models properly captures the protective behaviours reflected across multiple resolutions, from genes to humans. □

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