Allostasis, Homeostasis, and the Costs of Physiological Adaptation

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Contents

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1 Principles of Allostasis: Optimal Design, Predictive Regulation, Pathophysiology, and Rational Therapeutics[1,2]

Peter Sterling

INTRODUCTION

This chapter compares two alternative models of physiological regulation. The first model, *homeostasis* ("stability through constancy"), has dominated physiology and medicine since Claude Bernard declared, "All the vital mechanisms . . . have only one object – to preserve constant the conditions of . . . the internal environment." His dictum has been interpreted literally to mean that the purpose of physiological regulation is to clamp each internal parameter at a "setpoint" by sensing errors and correcting them with negative feedback (Fig. 1.1; Cannon, 1935). Based on this model, physicians reason that when a parameter deviates from its setpoint value, some internal mechanism must be broken. Consequently, they design therapies to restore the "inappropriate" value to "normal."

The homeostasis model has contributed immeasurably to the theory and practice of scientific medicine, so to criticize it might almost seem absurd. Yet all scientific models eventually encounter new facts that do not fit, and this is now the case for homeostasis. In physiology, evidence accumulates that parameters are *not* constant. Their variations, rather than signifying error, are apparently designed to *reduce* error. In medicine, major diseases now rise in prevalence, such as essential hypertension and type 2 diabetes, whose

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[1] This essay is dedicated to the memory of Howard A. Schneiderman, who recruited me to experimental biology and bailed me out of a Mississippi jail.

[2] Collected essays on this and related topics are available at http://retina.anatomy.upenn.edu/allostasis/allostasis.html

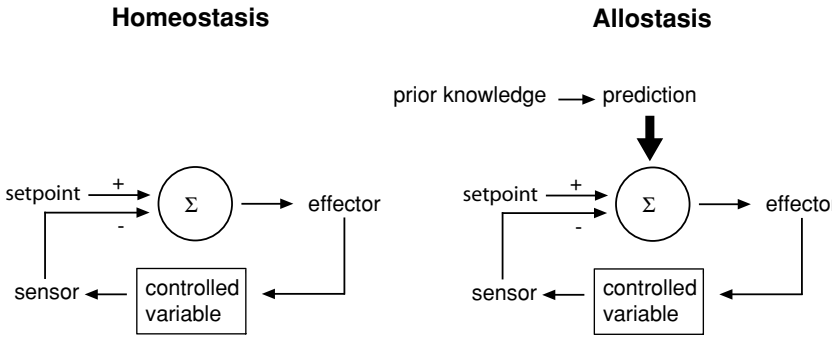

Figure 1.1: Alternative models of regulation. Homeostasis describes mechanisms that hold constant a controlled variable by sensing its deviation from a "setpoint" and feeding back to correct the error. Allostasis describes mechanisms that *change* the controlled variable by predicting what level will be needed and then overriding local feedback to meet anticipated demand.

causes the homeostasis model cannot explain. For in contrast to the hypertension caused by a constricted renal artery and the diabetes caused by immune destruction of insulin-secreting cells, these newer disorders present no obviously defective mechanism. Treating them with drugs to fix low-level mechanisms that are not broken turns out not to work particularly well. The chapter expands on each of these points.

The second model, *allostasis* ("stability through change"), takes virtually the opposite view. It suggests that the goal of regulation is *not* constancy, but rather fitness under natural selection. Fitness constrains regulation to be efficient, which implies preventing errors and minimizing costs. Both needs are best accomplished by using prior information to predict demand and then adjusting all parameters to meet it (Fig. 1.1). Thus allostasis considers an unusual parameter value not as a failure to defend a setpoint, but as a response to some prediction. The model attributes diseases such as essential hypertension and type 2 diabetes to sustained neural signals that arise from unsatisfactory social interactions. Consequently, the allostasis model would redirect therapy away from manipulating low-level mechanisms and toward improving higher levels to restore predictive fluctuation, which under this model is the hallmark of health.

This essay comprises six main sections. The first provides a capsule history of the allostasis model, which by now extends back over 40 years. The second section offers a brief critique of the homeostasis model, focusing on blood pressure because of its broad medical significance. The third section presents key principles of allostasis. Introduced are recent concepts of optimal matching and adaptive regulation, which are then used to reconsider problems of human physiology, such as blood pressure. The fourth section

describes how allostasis depends on higher neural mechanisms, and the fifth section suggests how these mechanisms interact with certain aspects of modern social organization to generate some of the major modern diseases. The last section treats the question of where to intervene.

ORIGINS OF ALLOSTASIS

For several decades, I combined research and teaching in neuroscience with social activism. In the mid-1960s, canvassing door-to-door in the African American ghettos such as Central and Hough of Cleveland Ohio, I noticed that many people who answered my knock were partially paralyzed – faces sagging on one side, walking with a limp and a crutch. The cause was "stroke," a rare affliction in my own community, and one that I never encountered later when canvassing in white, upper-class Brookline, Massachusetts. What caused so many strokes, I wondered, and how might they be connected to Cleveland's racial segregation? Arriving around 1970 at the University of Pennsylvania, I found that Joseph Eyer, another biologist-activist, had assembled clear epidemiological evidence that stroke and heart disease, and their precursor hypertension, all accompany various forms of social disruption, including migration, industrialization, urbanization, segregation, unemployment, and divorce (Eyer 1975, 1977; Eyer and Sterling, 1977).

While publishing the epidemiological data, we began to investigate the possible biological mediators. The fury in Hough – which during the summer of 1966 exploded in riots and occupation by National Guard troops – would tend to activate Cannon's well-known, "fight-or-flight" system (sympathetic nerves and adrenal medulla) and Selye's "stress" system (hypothalamo-pituitary-adrenal cortex). But we were astonished by new evidence from fluorescence microscopy that all blood vessels are richly innervated by catecholamine nerve fibers and new evidence from electron microscopy that most endocrine cells are also innervated. For example, sympathetic nerves contact the kidney cells that secrete renin, and parasympathetic nerves contact the pancreas cells that secrete insulin. Recent work has shown that nerves even contact cells that form bone and scavenger cells (macrophages) that serve inflammation and immune surveillance (Flier, 2000; Bernik et al., 2002; Blalock, 2002; Takeda et al., 2002; Tracy, 2002). This suggested that the brain has close access to essentially every somatic cell.

Furthermore, John Mason measured multiple hormones in awake, behaving monkeys and found concerted shifts that made functional sense. A mild demand for focused attention raised hormones associated with catabolism and suppressed those associated with anabolism (Mason, 1968, 1971, 1972). Furthermore, prolonging these demands caused sustained

elevations of blood pressure (Harris et al., 1973). Mason concluded that the broad metabolic patterns over short and long time scales, and under mild as well as emergency conditions, are controlled by the brain. Subsequently, myriad studies of neuroendocrine control have supported this conclusion (Schulkin, 1999).

Back then, standard medicine attributed essential hypertension and atherosclerosis to excessive consumption of salt and fat – as though what people choose to eat were unrelated to their internal physiological and mental states. So it was compelling to learn that the peripheral hormones that raise blood pressure, such as angiotensin, aldosterone, and cortisol, also modulate brain regions that stimulate hunger for sodium (reviewed by Schulkin, 1999; Fluharty, 2002). Similarly, peripheral hormones that increase catabolism, such as cortisol, also modulate brain regions that stimulate hunger for energy-rich substrates – fat and carbohydrates (reviewed by Schulkin, 1999; Schwartz et al., 2000; Saper et al., 2002). Of course, such findings would not have surprised Pavlov, who had demonstrated early on the brain's anticipatory control over many phases of digestion, nor Richter, who had connected specific hungers to physiological regulation (Schulkin, 2003a, 2003b).

But to a social activist this seemed immensely relevant: if the brain regulates both physiology and its supporting behavior, then treatments directed only at the peripheral physiology would tend to be countered by the behavior. So, rather than clamp blood pressure at some "normal" value by diuretics, vasodilators, and beta-adrenergic antagonists (the main antihypertensive drugs of the 1970s and '80s), wouldn't it be better to reduce social and psychological disruption? That is, wouldn't it be better to address the higher-level signals that stimulate both the physiology and the behavior? We found a perfect example at the Philadelphia Child Guidance Clinic.

Diabetic children who experience chronic bouts of ketoacidosis had been widely treated with beta-adrenergic antagonists. This often proved ineffective, and it was hypothesized that the metabolic disturbance is induced by parental conflict expressed through the child ("who is right, Daddy or Mommy?"). This was directly observed in "stress interviews." The parents' fatty acid levels would rise but soon return toward baseline, whereas the child's would remain elevated for hours (Fig. 1.2A). Clearly, potent psychological demands were driving multiple physiological mechanisms to override the beta-adrenergic mechanism. Salvador Minuchin, the clinic director, described this as a poignant demonstration that "behavioral events among family members can be measured in the bloodstream of other family members" (Minuchin, 1974).

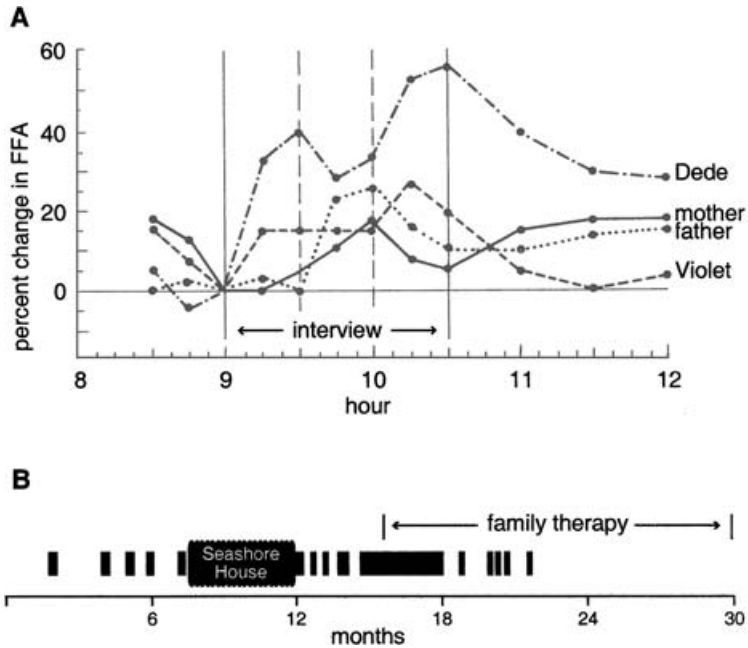

Figure 1.2: Parental conflict modulates a child's blood chemistry. **A.** While parents expressed conflict during an interview, free fatty acid levels rose in all family members. Initially the children, both diabetic, watched through a one-way mirror. At 10 o'clock, they entered the room, whereupon each parent tried to enlist Dede to take his or her side, while Violet remained aloof. Violet's free fatty acid levels followed the parents', but Dede's were greatly elevated. Reprinted from Minuchin, 1974. **B.** Child had been hospitalized (▌) for emergency treatment of ketoacidosis 23 times over 2 years, and beta-blocker treatment of her "superlabile" diabetes was unsuccessful. Family therapy that encouraged the parents to express their disagreements directly (rather than through the child) prevented further relapse. Modified from Baker et al., 1974.

Such children stabilized easily in the hospital but, upon reentering the family, soon relapsed. When the parents were helped to resolve their marital conflicts directly, the children stabilized at home without the beta-blocker (Fig. 1.2B; Baker et al., 1974). This example of successful intervention *between people,* rather than between nerve and liver, seemed of broad sociomedical significance (Sterling and Eyer, 1981). Nevertheless, the idea on which it rests, that the brain controls human physiology, remains largely outside the realm of standard teaching in biology and medicine.

Later, while summarizing this material for another essay collection, it hit us that when you *name* an idea, it has a better chance. So, we coined a new word, "allostasis," to emphasize two key points about regulation: *parameters vary,* and *variation anticipates demand* (Sterling and Eyer, 1988). The

idea did spread to some degree, largely through the prolific writings of experts on stress and neuroendocrine regulation, such as McEwen, Schulkin, Sapolsky, Koob, and their colleagues (Sapolsky, 1998; Koob and Le Moal, 2001; McEwen, 2002; Schulkin 2003a, 2003b). Yet even these proponents of allostasis have been somewhat reluctant to abandon homeostasis as the core theory of regulation and have tended to view allostasis as a modulator of homeostatic mechanisms. Some simply equated it with "stress" or "fight-flight" response and suggested that it is an anachronism. For example, "Allostasis has evolved as the response for running away from a predator, escaping acute danger, or fighting off a threat. . . . However, a defense system that has its roots in an archaic fish can be absurd in a modern human" (Elbert and Rochstroh, 2003). If this were allostasis, it would be entirely justified to discount it as just a fancy word applied to an old idea (Dallman, 2003).

But the allostasis model has a more radical intent – to *replace* homeostasis as the core model of physiological regulation. There are solid scientific reasons: the allostasis model connects easily with modern concepts in sensory physiology, neural computation, and optimal design. Also, this model can begin to comprehend what homeostasis cannot: the main diseases of modern society, such as hypertension, obesity-diabetes, and drug addiction. There are also practical, socially relevant reasons: the allostasis model suggests a different goal for therapeutics and thus a different direction for medical education and treatment. Consequently, this essay begins by assuming that the original conjecture is proved – that physiology is indeed sensitive to social relations. The evidence for this is now vast and thoroughly summarized by McEwen (2002), Sapolsky (1998), and Berkman and Kawachi, (2000). Thus I first describe some difficulties with the homeostasis model and then set out some core principles of the allostasis model that might justify the fancy name.

PROBLEMS WITH HOMEOSTASIS AS THE PRIMARY MODEL FOR REGULATION

Constancy Is *Not* a Fundamental Condition for Life

It seems past time to acknowledge that when Bernard declared constancy to be the sole object of all vital mechanisms, he went too far. Most biologists now agree that the true object of all the vital mechanisms is not "constancy" but survival to reproduce. So what all the vital mechanisms actually serve is reproductive success under natural selection. Moreover, there is nothing magical about "constancy." We now know that the conditions extend to amazing extremes: thermophilic bacteria can thrive at 100°C, and the limit

for their successful culturing extends to 113°C! (Hochachka and Somero, 2002). Cell temperatures in the desert can fluctuate by nearly 100°C, and even in complex metazoans the pH of blood and cytosol varies systematically with temperature (Hochachka and Somero, 2002).

Of course, some parameters are regulated quite closely. For example, the mammalian brain tolerates only small fluctuations in oxygen, glucose, temperature, and osmotic pressure. An acute insult that drives any one of these parameters beyond its design limit can trigger cascades of positive feedback that are quickly lethal. Such catastrophic departures from stability certainly require emergency treatment directed at low-level processes (Buchman, 2002). But the purpose of such tight regulation may not be to defend "constancy" in the abstract. Rather, it may simply reflect specific design choices that optimize overall mammalian performance for successful competition.

For example mammalian brain tissue, such as the intact retina or a slice of cerebral cortex, functions for hours in a simple medium at *room temperature*. A neuron's sensitivity is lower than for the optimal 37°C by twofold for each 10 degrees (Dhingra et al., 2003), similar to the temperature sensitivity of most biochemical reactions. So the mammalian brain's normal operating temperature apparently reflects an early design decision: to move fast, we must think fast. This decision had myriad consequences; for example, to move fast, we must also *see* fast. This requires the photoreceptors to be small, which in turn sets the design of retinal circuits (Sterling, 2004). In short, close regulation of human cerebral temperature does not exemplify *the* condition for preserving *all* life – it is just one condition set by a particular design.

A Mean Value Need Not Imply a Setpoint but Rather the Most Frequent Demand

It also seems past time to reevaluate the core hypothesis of the homeostasis model: that the average level of each parameter represents a "setpoint" that is "defended" against deviations (errors) by local feedback (Fig. 1.1). This model captured much of the experimental truth in a simple "preparation" – such as an isolated organ or an animal whose brain has been silenced by anesthesia or decerebration – which were the primary experimental models for more than 100 years. But regulation under natural conditions presents a response pattern that the homeostasis model cannot easily explain.

Consider the record of arterial blood pressure measured continuously over 24 hours in a normal adult (Fig. 1.3). Far from holding steady, pressure fluctuates markedly around 110/70 mm Hg for 2 hours. Then in correlation

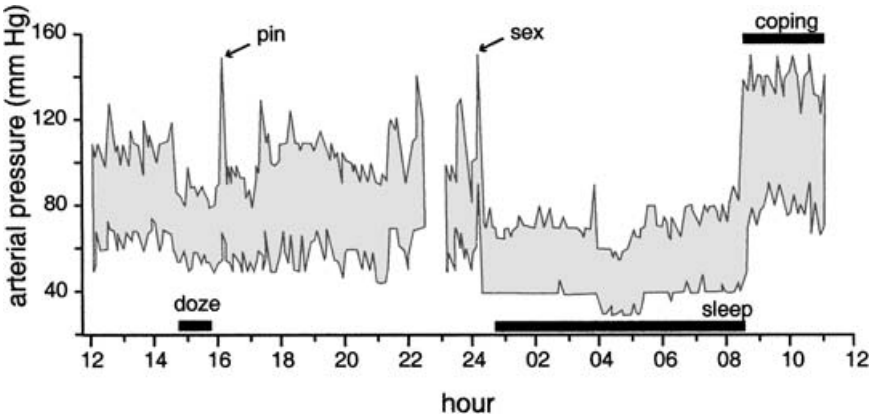

Figure 1.3: Arterial pressure fluctuates to meet predicted demand. Pressure was plotted in a normal adult at 5-minute intervals over 24 hours. Note that pressure spends about equal time above and below the steady daytime level. This pattern suggests not defense of a setpoint, but rather responsiveness to rising and falling demand. Upper trace, systolic; lower trace, diastolic. Redrawn from Bevan et al., 1969.

with identified external stimuli and mental states, it varies more extremely. As the subject dozes in lecture, pressure falls to 80/50. When he is jabbed with a pin, pressure spikes to 150/70; then, having recognized the prank, he again relaxes, and the pressure sinks to 80/50. During sexual intercourse, pressure spikes to 170/90 and then falls profoundly during sleep to ~70/40 with 1 hour as low as 55/30. In the morning, pressure steps up nearly to its level during sex and remains high for hours.

This record contains no hint that blood pressure is defended at particular setpoint. Quite the contrary, it fluctuates markedly and does so on multiple time scales – minutes, seconds, and hours. There are elevations, both brief and sustained, above the most frequent level. There are also similar depressions below the most frequent level. If this level truly represented a setpoint, we might expect it to fluctuate only mildly except when a particularly arousing signal would drive it higher (fight or flight). But the pressure spends about as much time *far below* the most frequent level as above it, and this is not predicted by a model of setpoint + arousal-evoked elevation. If fluctuations were caused by poor control, for example, by excessive or insufficient loop gain (Fig. 1.1), the deviations would show characteristic temporal patterns, such as "ringing" or lag. But the varied temporal patterns and their exquisite matching to particular behavioral and neural states imply that fluctuations arise not from poor control but from *precise* control.

Most parsimoniously, the record suggests that pressure is regulated to match anticipated demand, rising to certain signals and falling to others.

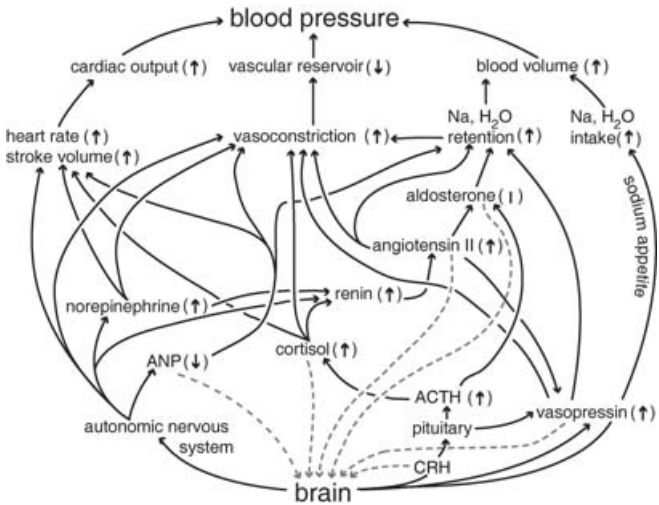

Figure 1.4: The brain sets blood pressure via multiple, mutually reinforcing mechanisms. Negative feedback mechanisms are acutely overridden. When demand persists, all mechanisms are reset to operate at the new level. Most hormones illustrated here are also sensed by the brain (dashed arrows) in specific regions that control behaviors supporting increased pressure. Thus, aldosterone and angiotensin II are sensed by brain regions that enhance salt appetite and drive salt-seeking behavior. CRH = corticotrophic releasing hormone; ACTH = corticotropin; ANP = atrionatiuretic peptide. Modified from Sterling and Eyer, 1988.

This implies that the most frequent value, 110/70, occurs not because pressure is clamped there, but because that value satisfies the most frequent level of demand (see Fig. 1.5). Indeed, were pressure actually clamped at an average value, it would match some specific need only by sheer accident. This is true for all states and all parameters: average values are useless. The essential need is to occupy distinctly different states and to move flexibly between them. But how could this occur, given local negative feedback mechanisms that do tend to resist fluctuations?

Once the brain predicts the most likely demand for oxygen, it resets the blood pressure to achieve the needed flow rate. Pressure here plays the same role as in a shower: for a given resistance, set by the caliber of all the channels, pressure sets the flow. To adjust the pressure, the brain directly modulates all three primary effectors: nerves signal the heart to pump faster, some blood vessels to constrict and others to dilate, and kidneys to retain salt and water. These direct neural messages are reinforced by additional signals acting in parallel (Fig. 1.4). For example, the neural system that excites the primary effectors also releases multiple hormones that send the same message. Hormones signaling the opposite message are suppressed. This pattern: multiple, mutually reinforcing signals acting on multiple, mutually

reinforcing effectors, overrides the various feedbacks that oppose change.[3] Recognizing such fluctuation, some authors have proposed the idea of shifting setpoints, termed "rheostasis" (Mrosovsky, 1990). Shifting setpoints might seem to describe certain cases, for example, sustained elevation of body temperature in fever, but even here temperature is responding to specific signals that fluctuate adaptively.

The same is true for essentially *all* parameters: temperature, blood distribution, hormone levels, and so on. All fluctuate with different amplitudes and time constants, and these fluctuations all share a single goal. Yet the goal is not constancy, but coordinated variation to optimize performance at the least cost. This is the core idea of allostasis, the essential principles of which are addressed next.

PRINCIPLES OF ALLOSTASIS (PREDICTIVE REGULATION)

This section discusses six interrelated principles that underlie allostasis: (1) organisms are designed for efficiency, (2) efficiency requires reciprocal trade-offs, (3) efficiency requires predicting what will be needed, (4) prediction requires each sensor to adapt its sensitivity to the expected range of input, (5) prediction requires each effector to adapt its output to the expected range of demand, and (6) predictive regulation depends on behavior whose neural mechanisms also adapt.

Organisms Are Designed for Efficiency

Organisms must operate efficiently. Beyond escaping predators and resisting parasites, they must compete effectively with conspecifics. If you encounter a bear while hiking with a friend, you need not outrun the bear – just your friend. So natural selection sculpts every physiological system to meet the loads that it will most likely encounter in a particular niche plus a modest safety factor for the unusual load. No system can be "overdesigned" because robustness to very improbable loads will slow the organism and raise fuel costs. Nor can a system be "underdesigned" because, if it fails catastrophically to a commonly encountered load, well, that's it. In effect the organism

[3] It is probably no accident that the error-correction model that Bernard adopted for physiology mimicked the simple device that inaugurated the 19th century's industrial technology (the speed governor on Fulton's steam engine). But machines have evolved, and the 21st century automobile now preempts driver errors. The myriad sensors in a BMW (~100) relay data to a central mechanism (computer chip) that calculates the power and braking needed by each wheel to optimize stability and skid resistance. Data from other sensors are centrally integrated to control fuel, oxygen, and spark timing for each cylinder to optimize fuel consumption at each power level. This resembles biology, where changing gait maximizes efficiency at different speeds (Alexander, 1996; Weibel, 2000). In short, for a car with a "brain," predictive regulation produces better stability and greater efficiency.

resembles an elevator cable, which must be just sufficiently robust to prevent the cancellation of the manufacturer's insurance (Diamond, 1993).

It follows that all internal systems should mutually match their capacities. Thus our intestinal absorptive capacity supplies sufficient fuel for our most likely energy need – with modest excess to meet unusual demands (Hammond and Diamond, 1997). Our lung and circulatory capacities supply sufficient oxygen to burn the available fuel; and our muscles contain sufficient mitochondrial capacity to provide an adequate furnace (Weibel, 2000). Clearly it would be inefficient for an organ to provide more capacity than could be used downstream, or for an organ downstream to provide more capacity than can be supplied from upstream. This aspect of organismal design, where physiological capacities optimally match, is termed "symmorphosis" (Taylor and Weibel, 1981). It holds for digestive, respiratory, and muscular systems, and also for neural systems (Diamond, 1993; Weibel, 2000; Sterling, 2004).

Efficiency Requires Reciprocal Trade-Offs

Efficiency requires that resources be shared. Otherwise, each organ could meet an unusual demand only by maintaining its own reserve capacity. To support this extra capacity would require more fuel and more blood – and thus more digestive capacity, a larger heart, and so on, thereby creating an expensive infrastructure to be used only rarely. Consequently, organs can trade resources – that is, make short-term loans. Regulation based on reciprocal sharing between organs is efficient, but for several reasons it requires a centralized mechanism: (1) to continuously monitor all the organs, (2) to compute and update the list of priorities, and (3) to enforce the priorities by overriding all the local mechanisms (Fig. 1.4).[4]

For example, skeletal muscle at rest uses about 1.2 liters of blood per minute (~20% of resting cardiac output), but during peak effort it uses about 22 L/min (~90% of peak cardiac output), an 18-fold increase. Much of the extra blood comes from increased cardiac output, but that is insufficient. And although tissues may store fuel, such as glycogen and fatty acids, they cannot store much oxygen. Nor would it be useful to maintain a large reservoir of deoxygenated blood because peak demand completely occupies the pulmonary system's capacity to reoxygenate. So a reservoir of deoxygenated blood would require a reservoir of lung, heart, and so on.

[4] Again, industrial analogies seem pertinent. Consider the efficiencies achieved by sharing electricity in a power grid and by rapidly redistributing inventory in a factory system. This type of efficiency requires continual, rapid updating of information about current demand, plus prior knowledge of how demand will probably change with factors such as temperature, time of day, season, world market, and so on.

In turn, these would require increased capacities for digestion, absorption, excretion, and cooling. Consequently, for an unstorable resource, subject to variable demand, it is most efficient to share. So, at peak demand about 10% of the total flow to muscle is *borrowed* (Weibel, 2000).

The loan cannot come from the brain, which requires a constant supply, that, if interrupted for mere seconds, causes loss of consciousness. So muscle borrows from the renal and splanchnic circulations, whose individual shares of cardiac output drop from about 20% to 1%, and whose absolute supplies fall by four- to fivefold (Weibel, 2000, figure 8.6). The skin circulation also contributes. Kidney, gut, liver, and skin can generally afford to lend for the short term – depending on circumstances. For example, skin can postpone reoxygenation, but during exercise in a warm environment it requires more blood for cooling. The gut can also postpone reoxygenation, but following a meal it requires more blood to transport digests into the portal circulation.

Reciprocity Requires Central Control

The brain, although it represents 2% by weight in a 70-kilogram man, requires 20% of the resting blood flow. This proportion is so great that when a given brain region increases activity, the extra blood is requisitioned not from somatic tissues, but from other brain regions (Lennie, 2003). Thus, within the brain itself, resources are reciprocally shared.

Because the needs of muscle, gut, and skin can be irreconcilable, appropriate trade-offs between them (and all the organs) must be calculated. This requires a central mechanism, the brain, which must also enforce a specific hierarchy of priorities and shift them as needs change. When muscular effort is urgent, but you have just eaten and the environment is warm, the brain triggers a vomiting reflex; when cooling is more urgent than effort, the brain may reduce the priority for an erect body posture and trigger the vasovagal reflex ("fainting"): the heart slows, vessels dilate, blood pressure falls, and muscle tone collapses. In short, the brain must decide the conditions for each loan and set the schedule for repayment. Furthermore, because such conflicts potentially threaten overall stability (survival), these solutions are accompanied by unpleasant sensations, such as nausea and dizziness, which the brain also provides. These sensations are vividly remembered to reduce the likelihood of repetition.

Efficiency Requires Predicting What Will Be Needed

We have already seen that blood pressure fluctuates to match the ever-shifting prediction of what might be needed (Fig. 1.3). This is true for essentially all physiological mechanisms. Consider an additional example, control of blood glucose by insulin.

This is usually presented as a core example of homeostasis: ingested glucose raises the blood level, stimulating pancreatic beta cells to release insulin, which stimulates muscle and fat cells to take up the glucose and restore blood levels to the standard ~90 mg/dL. Indeed a pancreas placed in vitro and exposed to glucose will release insulin. But when an intact person sits down to a meal, the sight, smell, and taste of food predict that blood glucose will soon rise, and this triggers insulin release via neural mechanisms *well before* freshly ingested glucose reaches the blood (Schwartz et al., 2000). This anticipatory pulse of insulin signals muscle and fat cells to take up glucose and signals the liver to cease releasing it. Thus this prediction can prevent a large rise in blood glucose.

A different prediction can do the opposite, that is, it can elevate blood glucose above the most frequent level. For example, Cannon reported that members of the Harvard football team, anticipating a game, would elevate their blood glucose to levels that spilled into the urine (Cannon, 1920). In other words, predicting an intense need for metabolic energy can raise blood glucose to diabetic levels. Insulin and the myriad other hormones that regulate the fuel supply are modulated rigorously from the brain, which bases its predictions on a continuous data stream regarding metabolic state that arrives via nerves from the liver and sensors in the cerebrovascular organs, such as the area postrema and the hypothalamus (Friedman et al., 1998; Saper et al., 2002). The importance and challenge of predictive regulation is best appreciated by the type 1 diabetic who, to minimize surges of blood glucose, injects insulin *before* a meal, and who, to allow his muscles to admit glucose, injects insulin *before* exercise.

Sensors Must Match the Expected Range of Input

Sensors are designed to transduce a range of inputs into a range of outputs (Fig. 1.5, upper panel). Typically the input-output curve is sigmoid and set so that its midpoint corresponds to the statistically most probable input (Fig. 1.5, lower panel). The curve's steep, linear region brackets a range of inputs that are somewhat likely, and its flatter regions correspond to inputs (very weak or very strong) that are relatively unlikely (Laughlin, 1981). This design has a clear advantage: the most likely events are treated with greatest sensitivity and precision (Laughlin, 1981; Koshland et al., 1982). When input events are small relative to noise, they may be amplified nonlinearly to remove the noise by thresholding (Field and Rieke, 2002), but most sensors amplify linearly as shown here (Rieke et al., 1999). Note that the design of each sensor embodies "prior knowledge," derived via natural selection, regarding the range of the most likely inputs (Sterling, 2004).

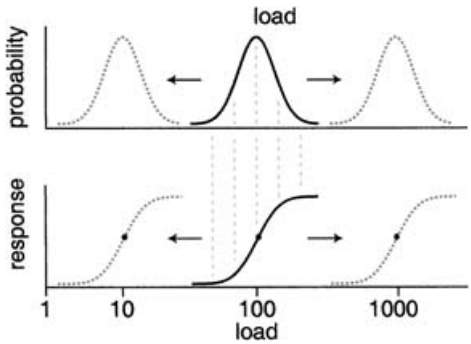

Figure 1.5: Regulatory mechanisms adapt to keep the input-output curves centered on the most probable loads. **Upper panel.** Every system confronts some distribution of probable loads (bold curve). As conditions shift, so does the distribution (dashed). **Lower panel.** The input-output curve (bold) is typically sigmoid with its most sensitive region (steep part) matched to the most probable loads. When the distribution of probable loads shifts, the input-output curve shifts correspondingly (dashed). See Laughlin, 1981.

This simple design is effective when the statistical distribution of inputs is steady. But environmental signals fluctuate enormously; for example, light intensity changes between day and night by 10-billion-fold. The linear range of a visual sensor spans only 10-fold, so over the course of a day, the sensor would frequently confront a range of inputs far too large or too small for its response curve (Fig. 1.5, lower panel). For much stronger inputs, the sensor would be too sensitive, and its output would saturate; for much weaker inputs, it would be too insensitive and would miss them.

There is a remedy: sense the altered input statistics → calculate a new probability distribution → shift the response curve to rematch its steep region to the most likely loads (Fig. 1.5, lower panel). This strategy for continually rematching outputs to expected inputs has been observed at all levels of biological organization, from bacteria and somatic (nonneural) cells to neurons (Sakmann and Creutzfeldt, 1969; Koshland, 1987). At lower levels, the process has been termed "adaptation," and recently "Bayesian" has been added to emphasize Bayes's insight that the best estimate of what is happening in the world combines data from our sensors with our prior knowledge about what is probably out there (Rieke et al., 1999). This principle operates at many levels. Thus, we rely on a single experience of the unpleasant sensations associated with regulatory conflict (dizziness, nausea) to permanently enlarge our store of "prior knowledge." And in the perceptual realm, we identify an ambiguous object by sight or touch by combining sensory inputs with our prior knowledge of what the context suggests is most likely (Geisler and Diehl, 2002, 2003). In case of conflict