Mathematical Biosciences 257 (2014) 104–110

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Escape from homeostasis

H. Frederik Nijhout [a,*], Janet Best [b,1], Michael C. Reed [b]

[a] Department of Biology, Duke University, Durham, NC 27705, USA
[b] Department of Mathematics, Duke University, Durham, NC 27705, USA

ARTICLE INFO

Article history:
Available online 19 September 2014

Keywords:
Thermoregulation
Homocysteine
Dopamine
Myogenic response
Feed forward inhibition
Chair curve

ABSTRACT

Many physiological systems, from gene networks to biochemistry to whole organism physiology, exhibit homeostatic mechanisms that keep certain variables within a fairly narrow range. Because homeostatic mechanisms buffer traits against environmental and genetic variation they allow the accumulation of cryptic genetic variation. Homeostatic mechanisms are never perfect and can be destabilized by mutations in genes that alter the kinetics of the underlying mechanism. We use mathematical models to study five diverse mechanisms of homeostasis: thermoregulation; maintenance of homocysteine concentration; neural control by a feed forward circuit; the myogenic response in the kidney; and regulation of extracellular dopamine levels in the brain. In all these cases there are homeostatic regions where the trait is relatively insensitive to genetic or environmental variation, flanked by regions where it is sensitive. Moreover, mutations or environmental changes can place an individual closer to the edge of the homeostatic region, thus predisposing that individual to deleterious effects caused by additional mutations or environmental changes. Mutations and environmental variables can also reduce the size of the homeostatic region, thus releasing potentially deleterious cryptic genetic variation. These considerations of mutations, environment, homeostasis, and escape from homeostasis help to explain why the etiology of so many diseases is complex.

1. Introduction

Humans, as all other organisms, are subject to a great deal of genetic and environmental variation. Yet our phenotypes are remarkably robust to those perturbations. The stability against environmental fluctuations is maintained dynamically by homeostatic mechanisms that activate a variety of compensatory processes. Homeostatic mechanisms therefore allow us to adapt to a large range of environments and to daily and seasonal fluctuations in environmental variables such as nutrition and temperature.

Homeostatic mechanisms also stabilize phenotypes against genetic variation [1–4]. These processes mask the deleterious effects of mutations and thus allow the accumulation of mutations that might otherwise cause disease. These continually accumulating mutations are referred to as cryptic genetic variation [5]. When a homeostasis mechanism is disrupted by a mutation, then environmental variation and cryptic genetic variation are no longer buffered and this can result in aberrant, variable and unstable phenotypes. Deleterious mutations are no longer masked, and this is believed to be the underlying cause of many complex diseases [5,6].

The mechanisms that stabilize phenotypes against environmental and genetic variation are diverse and operate at the genetic, biochemical, physiological and behavioral levels. All these mechanisms result in a chair-shaped response curve to environmental or genetic variation: the trait initially rises with increasing values of the independent variable, then there is a range over which the mechanism is able to stabilize the trait, but the trait then rises again with further increase of the genetic or environmental variable. Mutations in the homeostatic mechanism either reduce the range over which the trait is stable or make the trait less stable over the entire range of environmental or genetic variation.

Here we use mathematical models to explore the properties of five very different homeostatic mechanisms: mammalian thermoregulation, maintenance of homocysteine concentration in the liver, feed-forward inhibition in a neural circuit, the myogenic response in kidneys, and regulation of extracellular dopamine concentration in the brain. In each case, there is a range of genetic or environmental variation in which the trait is stable and adjacent regions where it is not. In the case of dopamine we show that much of the standing genetic variation occurs within the homeostatic region where mutations have little effect on the dopamine concen-

* Corresponding author.
E-mail address: hfn@duke.edu (H.F. Nijhout).
[1] Permanent address: Department of Mathematics, The Ohio State University, Columbus, OH 43210, USA.

http://dx.doi.org/10.1016/j.mbs.2014.08.015
0025-5564/

tration. We illustrate how the stable homeostatic region can be reduced or eliminated by simple changes in the underlying mechanism.

2. Results

2.1. Thermoregulation

This is the classical example of a homeostatic system. Experimental data show that body temperature in mammals remains quite constant over a large range of environmental temperatures. Body temperature is regulated by the hypothalamus, which receives information about blood temperature and skin temperature and regulates metabolic rate, peripheral vasoconstriction, piloerection, shivering and sweating, as appropriate, to bring temperature back to a set-point. These regulatory mechanisms are unable to buffer body temperature at both extremely low and extremely high environmental temperatures. A simple mathematical model of thermoregulation with saturating heating and cooling mechanisms is given by:

$$\frac{dBT}{dt} = k_1(envT - BT) + k_2 + \frac{k_3(setp - BT)^+}{k_4(setp - BT)^+} - \frac{k_5(BT - setp)^+}{k_6(BT - setp)^+} \qquad (1)$$

The first term gives the rate of heating or cooling as the difference between environmental temperature (*envT*) and body temperature (*BT*); the second term is the rate of endogenous metabolic heat production, the third and fourth terms are saturating functions that set the rates of heating and cooling, respectively, controlled by the difference between body temperature and a set-point (*setp*). The parameter k_1 sets the rate of conductive gain or loss and parameters k_2–k_5 determine the shape of the response. For each choice of *envT*, we solve the differential equation and let it relax to equilibrium. A graph of the equilibrium temperature *BT* as function of *envT* is shown in Fig. 1A, which we compare to experimental data from the brown opossum [7]. Parameters were chosen so that the curve fits the data well. If the heating and cooling terms were not there, then at steady state *BT* would be a linearly increasing function of *envT*. With the heating and cooling terms present, there is a wide plateau region because the heating and cooling terms automatically compensate for the changes in environmental temperature. This homeostatic mechanism works well over a wide range of environmental temperatures but breaks down below 12 °C and above 30 °C. Notice that the brown opossum tries to thermoregulate to 34 °C, but once the environmental temperature reaches 30 °C it begins to lose control due to metabolic heat production. Mutations that reduce the activity of the heating or cooling mechanism narrow the stability plateau of the chair curve (Fig. 1B).

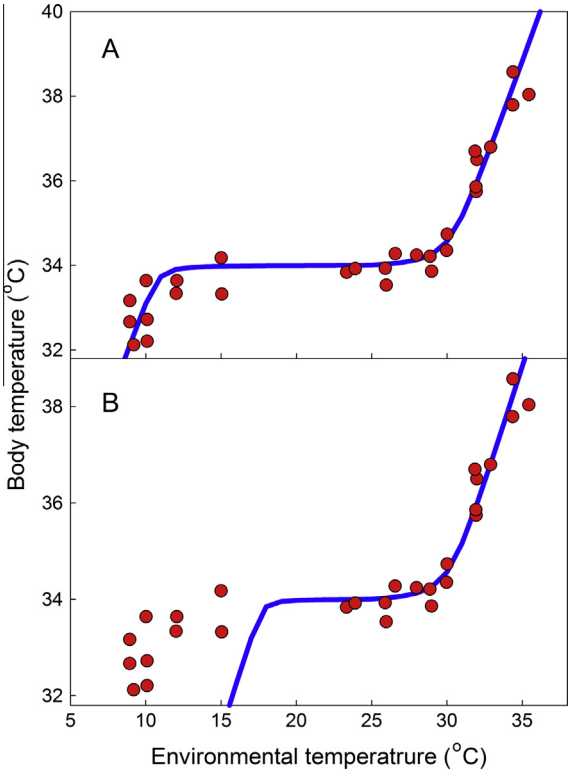

Fig. 1. Thermoregulatory homeostasis in the brown opossum. A. Data are shown by circles and the model calculations from Eq. (1) are shown by the chair-shaped curve. Parameter values were: *setp* = 34, k_1 = 2.15, k_2 = 20, k_3 = 30, k_4 = 0.01, k_5 = 12, k_6 = 0.1. B. A reduction in the efficacy of the heater (k_3 = 15) narrows the range of environmental temperatures over which body temperature can be maintained.

2.2. Homeostasis of homocysteine concentrations

Homocysteine (Hcy) is a metabolite that is produced from methionine in the methionine cycle (see Fig. 2). Some homocysteine is remethylated to form methionine and some enters the transsulfuration pathway (CBS reaction) that manufactures glutathione (GSH), the major anti-oxidant in cells. The importance of Hcy is that high levels of Hcy in the plasma or the urine have been clearly associated with adverse cardio-vascular events, though the exact causal mechanisms have not been determined [8]. The concentration of Hcy in the liver is affected by the input of methionine, which varies with each protein meal, and is also affected by folate (vitamin B9) because folate, in the form of 5-methyltetrahydrofolate (5mTHF), is a substrate for the reaction that remethylates Hcy to methionine [9]. Thus elevated input of methionine tends to raise Hcy and an elevated level of folate tends to reduce the concentration of Hcy.

The concentration of Hcy is stabilized by interesting homeostatic mechanisms that are due to long-range allosteric interactions (shown in red[2] in Fig. 2) between the folate cycle and the methionine cycle. That is, there are substrates in each cycle that inhibit enzymes in the other cycle. In [10], we showed that these long range interactions stabilize the flux of DNA methylation in the methionine cycle against fluctuations in methionine input due to meals. Here we use the mathematical model, corresponding to Fig. 2 and described in [11], to show that these same long-range interactions also stabilize the concentration of Hcy. When methionine input goes up, this increases the concentration of S-adenosylmethionine (SAM). Elevated levels of SAM have several consequences. SAM increases the activity of cystathionine-β-synthase (CBS), which increases removal of Hcy. SAM also inhibits the enzyme methylene tetrahydrofolate reductase (MTHFR), which reduces the concentration of 5mTHF. Since 5mTHF is a co-substrate for methionine synthase (MS) this reduces the rate of transformation of Hcy to methionine. A decrease in 5mTHF also increases the rate of the glycine methyltransferase (GNMT) reaction, which speeds up the production of Hcy. SAM also inhibits betaine-hydroxymethyltransferase (BHMT), which also reduces the rate at which Hcy is transformed into methionine. Together these reactions serve to increase the removal of Hcy from the system when methionine input goes up, and stabilize the Hcy concentration against fluctuations in methionine input.

[2] For interpretation of color in Fig. 2, the reader is referred to the web version of this article.

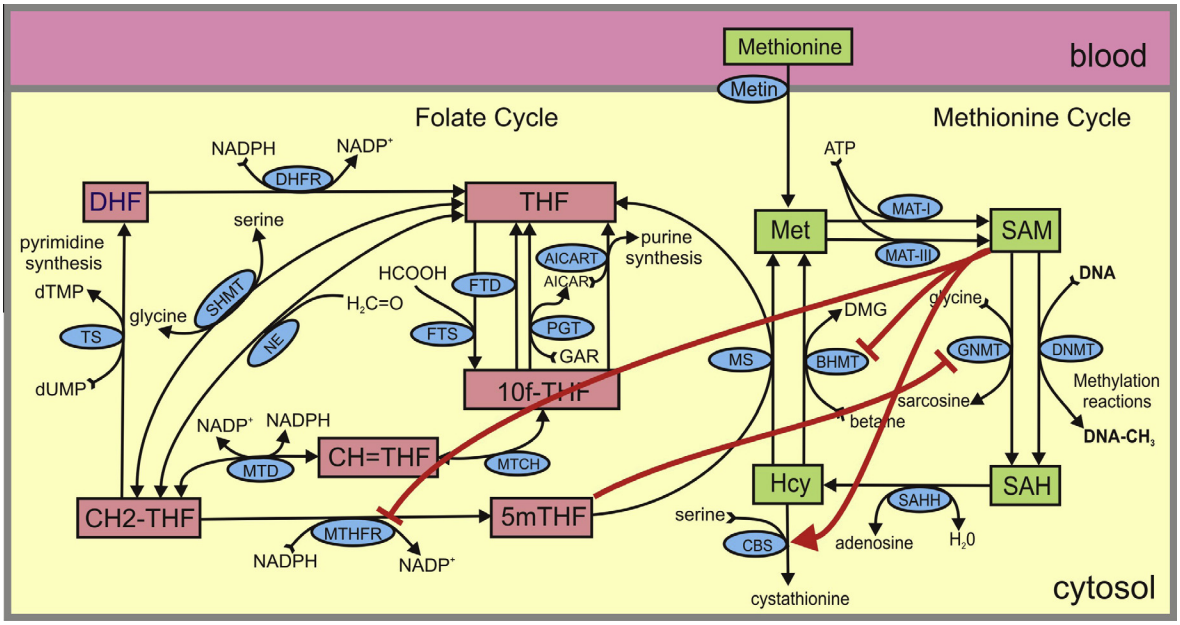

Fig. 2. Diagram of the folate and methionine cycles modeled in [10] and [11]. Ellipses represent enzymes and boxes are metabolites. Thin black arrows are biochemical reactions and the thick red arrows represent long-range allosteric activations and inhibitions of enzymes. Names and acronyms are given in [10] and [11].

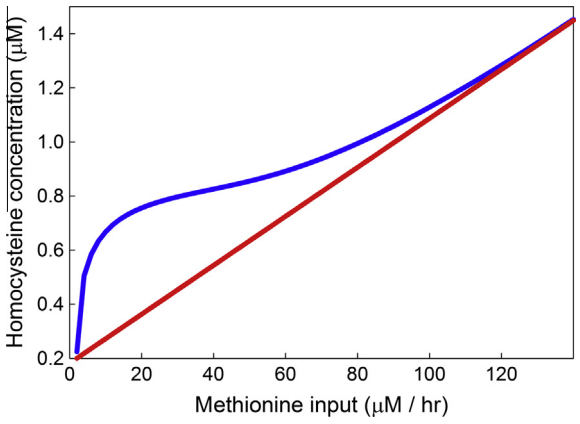

Fig. 3. Long-range interactions stabilize Hcy concentration in the liver. The curve shows the Hcy concentration at steady state as a function of methionine input when the long-range interactions are turned on. The line shows the analogous curve if the long-range interactions are turned off. Computations were made using the mathematical model in [11].

Fig. 3 shows the Hcy concentration at steady state as methionine input is varied from 0 to 150 μM/h when the long-range allosteric interactions shown in Fig. 2 are in place. Calculations were made by the mathematical model in [11]. For very small methionine input the Hcy curve rises rapidly. Then, for inputs between 20 and 100 μM/h, the Hcy concentration remains quite stable, but goes up again quickly as the methionine input rises above 100 μM/h. By contrast, the straight line in Fig. 3 shows the Hcy concentration as a function of methionine input if the long-range interactions are turned off; in this case there is no homeostasis and Hcy rises proportionally to the methionine input.

As in Section 2.1, the homeostatic region is bounded on either side by regions where the dependent variable, in this case Hcy, changes rapidly with variation in input. And, although most interest is focused on very high Hcy because of the connection to cardiovascular disease, it is also known that very low homocysteine also has deleterious effects. Hcy inhibits various anti-coagulant factors, so low Hcy may lead to slow clotting [12]. Low Hcy is associated

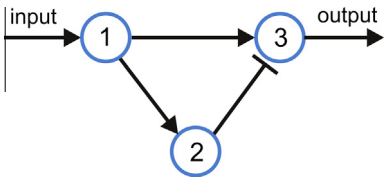

Fig. 4. A simple neural feed forward inhibition circuit.

with poor outcomes for hemodialysis patients [13]. Furthermore, very low Hcy means less production of GSH. And low GSH is associated with autistic disorder [14] and with the presence of AIDS [15]. So departure from the homeostatic region to either very high Hcy or very low Hcy appears connected to adverse health effects.

2.3. Homeostasis created by feed forward inhibition

The concept of feed forward inhibition has been known for a long time in biochemistry [16] and plays an important conceptual role in neuroscience where it is used in many circuit diagrams. The motif of feed forward inhibition is depicted in the neural setting in Fig. 4. The input excites neuron 1, which sends excitatory inputs to neuron 2 and neuron 3. Neuron 2 inhibits neuron 3. Thus neuron 3 receives excitatory input from neuron 1 and (feed forward) inhibition from neuron 2. In [17] the network in Fig. 4 is used for simultaneity detection and in [18] a collection of such networks are used to create a synchrony decoder. In [19], feed forward inhibition is used to explain homeostasis and plasticity in the developing nervous system.

We model the simple circuit in Fig. 4 as follows. Let x_1, x_2, and x_3 denote the firing rates of neurons 1, 2, and 3, respectively. We assume that x_1, x_2, and x_3 satisfy the differential equations:

$$\frac{dx_1}{dt} = I - x_1$$
$$\frac{dx_2}{dt} = \frac{V_2(x_1 - T)^+}{k_2(x_1 - T)^+} - x_2$$
$$\frac{dx_3}{dt} = \frac{V_3(x_1 - x_2)^+}{k_3(x_1 - x_2)^+} - x_3$$

where $(x–y)^+$ is zero if $x < y$, and is equal to $x–y$ otherwise. The decay term in the first equation means that, at steady state, neuron 1 will have a firing rate equal to its input I. The response of neuron 2 depends on neuron 1 in Michaelis–Menten fashion according to how much the input from neuron 1 exceeds the threshold T, and it has a maximal firing rate of V_2. Neuron 3 responds in Michaelis–Menten fashion to the amount that the excitatory input from neuron 1 exceeds the inhibitory input from neuron 2, and it has a maximal firing rate of V_3.

What will happen at steady state as we raise the input I? As we raise I from 0, neuron 3 will receive increasing positive input from neuron 1 and no inhibitory input from neuron 2 until the output of neuron 1 exceeds its threshold T, so the firing rate of neuron 3 will increase rapidly. Once the output of neuron 1 is over the threshold T, further increases in I should not change the firing rate of neuron 3 very much because the increased input from neuron 1 is countered by increased inhibition from neuron 2. If, however, neuron 2 has a smaller maximal firing rate than neuron 3, then eventually the inhibition from neuron 2 will be outstripped by increasing input from neuron 1 and the firing rate of neuron 3 should again start to rise rapidly. This is exactly the behavior that we see in Fig. 5 where we graph the steady state firing rate of neuron 3 as a function of the input I for a particular choice of parameters. As I starts to rise, the firing rate of neuron 3 rises rapidly and then plateaus as I increases further followed by increasing again at high input level. Thus one obtains a central homeostatic region bounded on either side by non-homeostatic regions just like the behavior we saw in Sections 2.1 and 2.2.

Of course the existence and width of the homeostatic region depends on the choice of parameters. Many neurons have maximal firing rates in the range 100–300 spikes/s; see, for example Fig. 9 in [20], which discusses the auditory nerve. And, there are many examples of neurons where the threshold T is quite large. Octopus cells in the cochlear nucleus receive 60–100 synapses from auditory nerve neurons and require that 20–50% of these synapses be activated within one msec in order to fire an action potential [21,22]. The above example was not intended to model an specific situation, but rather to explain why feed-forward inhibition can give rise to a homeostatic region in spike output.

2.4. Flow regulation in the kidney

In the kidney, plasma and small molecules are forced out of capillaries in the glomerulus of each nephron and enter the loop of Henle. For the mechanisms in the nephron that regulate salt and water balance in the body, it is important to control the flow in the afferent arteriole to each glomerulus. One of the ways in which this is done is by an active mechanism, the myogenic response, in the smooth muscle surrounding the afferent arteriole to each glomerulus. When the pressure is increased the stretching of the muscle membrane opens ion channels. The muscle cells become depolarized and a calcium signal causes the smooth muscle to contract increasing resistance and counteracting the increased flow that would result from higher pressure if the vascular wall responded passively. Thus, the myogenic response causes the flow in the afferent arteriole to remain relatively constant despite changes in pressure.

In a recent paper [23], Sgouralis and Layton show by using a mathematical model how well the myogenic response works. The blue curve in Fig. 6 shows the percentage change at steady state in their model as the pressure in the afferent arteriole is varied from 40 mmHg to 220 mmHg. The flow rate is remarkably stable between 90 mmHg and 190 mmHg. Below 90 mmHg the flow drops quickly and above 190 mmHg the flow begins to increase substantially giving the same chair-shaped curve that we have seen in previous sections. The green curve shows what the flow rate would be if the myogenic response were turned off and the walls of the arteriole responded passively. We note that the nephron has other mechanisms, for example tubuloglomerular feedback [24] for regulating flow in the afferent arteriole and glomerular filtration rate.

2.5. Homeostasis of extracellular dopamine

Dopamine is an important neurotransmitter in the brain that is linked to motivation, cognition, memory, and fine motor control [25–27]. Dysregulation of the dopamine system is associated with Parkinson's disease, Tourette's syndrome, Huntington's disease, attention deficit disorder, schizophrenia, and drug and alcohol abuse [28–31].

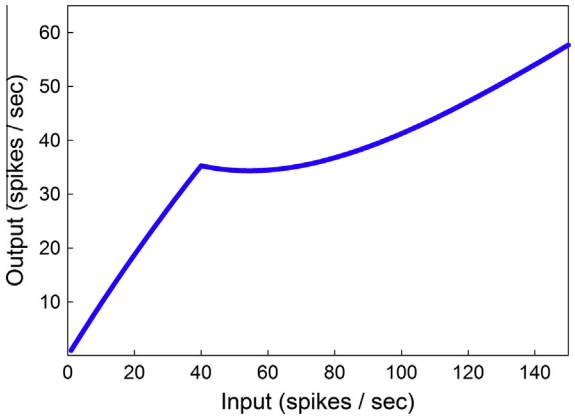

Fig. 5. Homeostatic behavior created by feed forward inhibition. The figure shows the firing rate of neuron 3 at steady state as the input I of neuron 1 is varied from 1 to 150. The parameters in the simulation were $T = 40$, $V_2 = 200$, $k_2 = 170$, $V_3 = 300$, $k_3 = 30$.

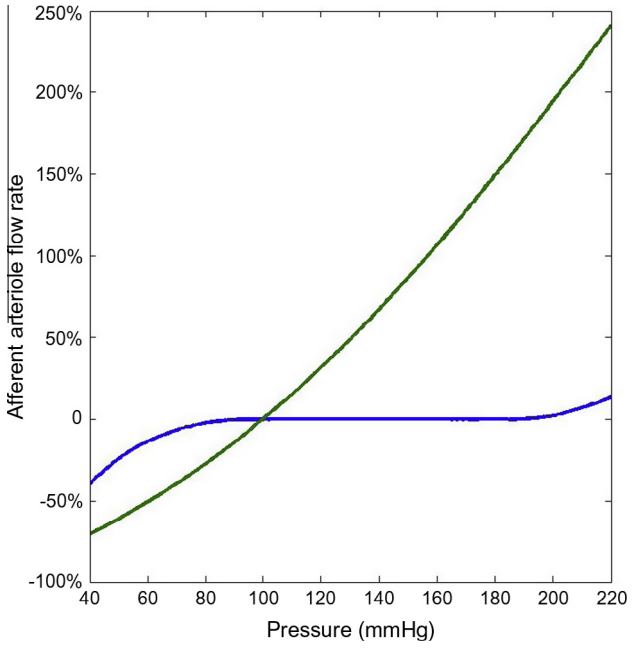

Fig. 6. Regulation of flow in renal afferent arterioles. The myogenic response in the smooth muscle enables nephrons to regulate flow in afferent arterioles over a wide range of pressures (blue curve). The y axis shows the percent change from normal flow at 100 mmHg as pressure varies. The green curve shows flow as a function of pressure if the myogenic response is turned off. The figure is redrawn from Fig. 4B in [23]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

A diagram for dopamine metabolism is shown in Fig. 7. In the terminals of dopaminergic neurons, dopamine (DA) is synthesized from the amino acid tyrosine (Tyr). Tyrosine is converted to l-dopa by the enzyme tyrosine hydroxylase (TH), and subsequently to cytosolic dopamine (cDA) by aromatic amino acid decarboxylase (AADC). Cytosolic dopamine is packaged into vesicles by the monoamine transporter (MAT), and stored as vesicular dopamine (vDA), which is released into the synaptic cleft when an action potential arrives at the terminal. The resulting extracellular DA (eDA) acts on postsynaptic receptors, and is also transported back into the terminal by dopamine transporters (DATs) [32]. Most dopamine terminals also have autoreceptors (auto) that sense the eDA concentration and affect the activity of TH and the release of vDA [27]. When eDA is low, TH activity and vDA release increase, thus increasing the synthesis and release of dopamine, and when eDA is high the activity of TH and release of dopamine from vesicles are inhibited. Thus, the autoreceptors create a homeostatic mechanism that stabilizes the eDA concentration and keeps it within a fairly narrow range. There are additional mechanisms such as substrate inhibition [33] that contribute to the stabilization of eDA [34]. Monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) break down intracellular and extracellular dopamine.

In [35] we created a mathematical model corresponding to the metabolic diagram in Fig. 7 and we will use that model here to illustrate how this homeostatic mechanism works in the face of variation in TH activity and DAT activity. Fig. 8 illustrates the effect of variation of TH and DAT activity on the concentration of eDA. Activity of TH and DAT and the concentration of eDA are represented as fractions of their normal value (where normal = 1). Notice that the eDA concentration is stable over a broad range of TH and DAT activities, as shown by the large plateau in Fig. 8. Point (1,1,1), indicated by the large white circle, shows the position of the normal or wild-type genotype. The smaller circles indicate the locations of several combinations of genetic polymorphisms of TH and DAT that occur in human populations. These polymorphisms raise or lower the activity of TH and lower the activity of the DAT as indicated in Table 1.

It is interesting that all of these genetic polymorphisms lie on the plateau. Presumably, this is because polymorphisms that would result in large changes in eDA are deleterious and would, therefore, be removed from the population. Thus, although the polymorphisms have large effects on the activities of TH and DAT, they have only a very small effect on the phenotypic variable eDA, and thus can be considered to be cryptic genetic variation.

The flatness of the plateau region depends on the autoreceptors mentioned above. If one removes the autoreceptor effect the resulting surface becomes much steeper (simulation not shown). With the autoreceptors included in the model, the maximal increase of eDA above normal, among all the polymorphisms, is 59%, and the maximal decrease is 37%. If the autoreceptor effects are removed, then the maximal increase was 109% and the maximal decrease was 62%. Thus mutations that affect the function of the autoreceptor can result in the release of potentially deleterious cryptic genetic variation.

This example is different from the ones in Sections 2.1–2.4 where a single parameter was varied and one had a plateau with rapid change on the margins of the plateau. Here there are two parameters being varied (TH and DAT) and one phenotypic variable, eDA. Thus one obtains a two-dimensional surface in 3-space. eDA plunges rapidly to zero when TH activity gets too small and

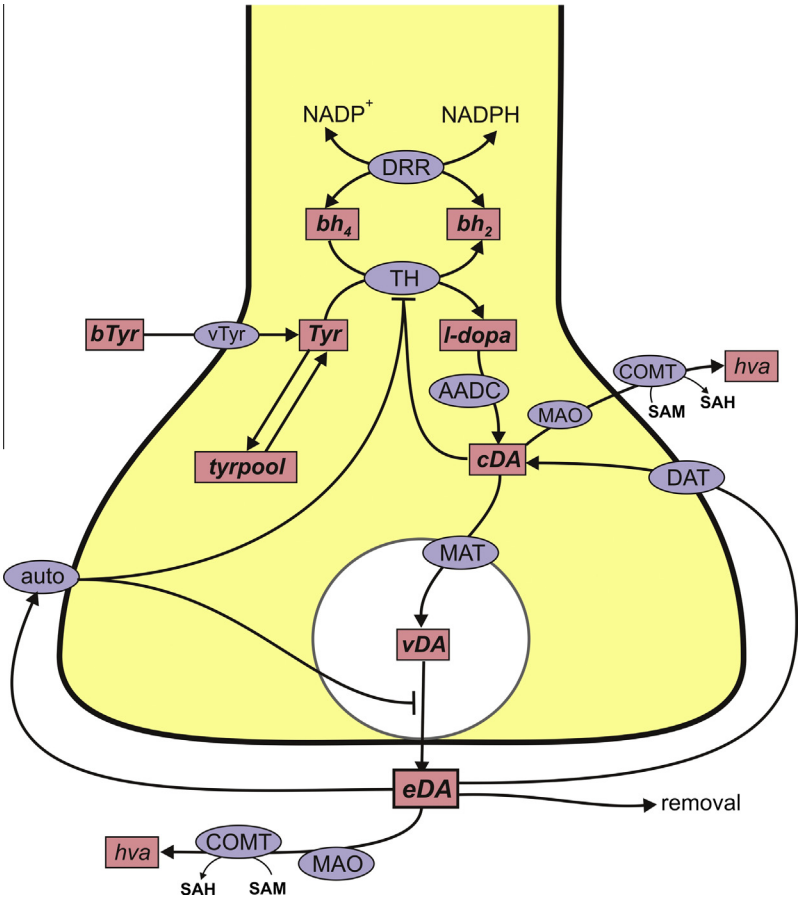

Fig. 7. The dopamine synthesis, release and re-uptake pathway in the terminal of a dopaminergic neuron. Ellipses indicate enzymes, receptors and transporters; rectangles indicate metabolites. Based on [35].

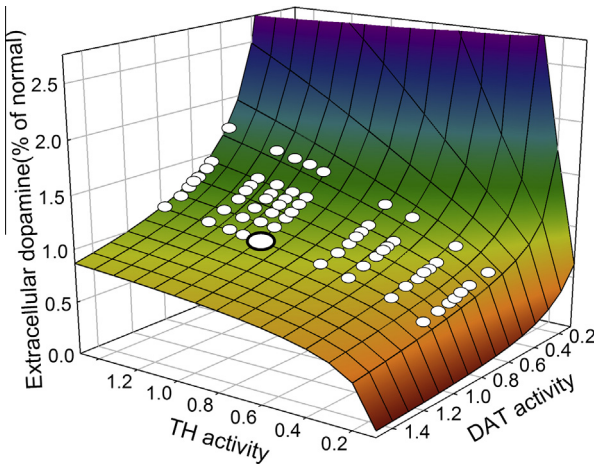

Fig. 8. Homeostasis of eDA in response to variation in the activities of TH and the DATs. The *x* and *y* axes show the fractional activity of TH and DATs (normal = 1). The *z* axis shows the fractional eDA concentrations (normal = 1) corresponding to each choice of fractional activity of TH and DATs. Computations were performed using the mathematical model in [35]. The autoreceptors create a large flat plateau around the wild-type genotype, indicated by the large white circle. The smaller white circles indicate the positions of the genotypes (homozygotes and heterozygotes) of the polymorphisms of TH and DAT in human populations indicated in Table 1.

Table 1
Polymorphisms in TH and the DAT plotted in Fig. 8.

Gene	Mutation to wild-type	Activity relative (%)	Source
TH	T245P	150	[36]
TH	T283M	24	[36]
TH	T463M	116	[36]
TH	Q381K	15	[37]
DAT	V382A	48	[38]
DAT	VNTR10	75	[38]
DAT	hNET	65	[39]

grows uncontrollably when DAT activity gets too small, so one leaves the homeostatic plateau by moving in those two orthogonal directions. We note that as one moves from (DAT = 1.5, TH = 0) to (DAT = 0, TH = 1.5) in a straight line in parameter space, then one obtains a chair-like graph, much as seen in Sections 2.1–2.4.

In Parkinson's disease, many motor symptoms are caused by very low eDA in the striatum of the basal ganglia, which, in turn, is caused by cell death of the dopaminergic neurons in the *substantia nigra pars compacta* (SNc) [27]. By contrast, the dyskinesias that may result from levodopa therapy are known to be caused by unusually high concentrations of eDA in the striatum [40]. The chorea of Huntington's disease is also associated with high concentrations of eDA in the striatum, that in turn may be caused by degeneration of inhibitory projections from the striatum to the SNc [41]. There is a hypothesis that hyperactivity of dopamine transmission underlies many of the symptoms of schizophrenia [31]. The fact that amphetamines, cocaine, and other drugs that increase levels of eDA cause similar symptoms to schizophrenia supports this hypothesis. These three diseases illustrate the idea that when one departs from the homeostatic region, either above or below, disease processes may occur.

3. Discussion

Many physiological systems, from gene networks to biochemistry to whole organism physiology, exhibit homeostatic mechanisms that keep certain variables within a fairly narrow range. Such is the case with the examples we have given in this paper. In Section 2.1 we gave a simple model of temperature regulation and in Section 2.2 we used a previously developed model of one-carbon metabolism to study the stability of homocysteine concentration in the liver under variable methionine input. In Section 2.3 we gave a simple prototype of a neural homeostatic mechanism and in Section 2.4 we studied the myogenic response in the kidney. In Section 2.5 we investigated the stability of extracellular dopamine in the face of variations in tyrosine hydroxylase and the dopamine reuptake transporters using a previously developed model of dopamine synthesis, release, and reuptake. Although these are very different physiological systems the results were similar. There is a homeostatic region in which variation of the independent variable(s) does not cause much change in the dependent variable. But outside that region, variation in the independent variable causes large changes in the dependent variable. The homeostatic region is necessarily finite because the compensatory mechanisms are themselves physiological processes that are limited by evaporation rates, maximal firing rates, V_{max} values of biochemical reactions, or binding rates.

We indicated in Section 2.2 that adverse health effects seem to occur when homocysteine is outside the homeostatic region. Similarly, in Section 2.5 we discussed that other adverse health effects occur when extracellular dopamine is too high or too low compared to normal. It has been suggested that disease processes occur when certain variables leave their homeostatic regions [6]. If we accept this hypothesis then Fig. 8 helps us understand what it means for a gene to "predispose" one for a certain disease. That is, the gene does not cause the disease, but people with the gene are more likely to get the disease, or may experience symptoms earlier, or be pushed more easily into the symptomatic region by variation in other causal factors. All of the polymorphisms indicated in Fig. 8 are on the homeostatic plateau, but some are much closer to the edge of the plateau than others. For individuals near the edge of the plateau, changes in other variables like diet, stress, lack of exercise, or environmental toxins may push the individual into the non-homeostatic regions starting a chain reaction that leads to the disease. The Q381K polymorphism in tyrosine hydroxylase is shown by the rightmost row of spots in Fig. 8, where the surface begins to drop off sharply. Individuals with this polymorphism show a levodopa-responsive dystonia, brought about by low levels of extracellular dopamine [37].

Each of the homeostatic mechanisms that we have discussed is imbedded in a large, complex, dynamic network of interactions and many other variables or processes can affect the homeostatic mechanisms. For example, we have shown [42] that the flux of the AICART reaction, important for DNA synthesis, is quite impervious to the activity of the enzymes TS and MTHFR in one carbon metabolism (see Fig. 2). However, in the presence of a folate deficiency, AICART flux is very dependent on MTHFR activity. That is, a folate deficiency strongly tilts the homeostatic surface. As a second example, we note that diabetes mellitus affects the myogenic response that we discussed in Section 2.4. In diabetic rats, the voltage gated calcium channels in the smooth muscle are impaired [43] and this greatly diminishes the range and effectiveness of the myogenic response [44]. That is, high blood sugar leads to a destabilization of the control of salt and water balance in the body. This is an example of how normal control mechanisms can be destabilized in disease states leading to further downstream consequences unrelated to the original cause of the disease. Thus, understanding homeostatic mechanisms in the full complexity of the body is very difficult.

Our work in cell metabolism has shown us that some homeostatic mechanisms are rather straightforward (like the autoreceptor effects on extracellular dopamine) and some are quite subtle (like the effects of the long range allosteric interactions in one carbon metabolism). It is not the case that when cellular inputs

change dramatically, for example after meals, that all variables are homeostatic. On the contrary, some variables change dramatically so that other variables (it is tempting to think of them as the important variables) can remain homeostatic [45]. These homeostatic effects typically depend on many independent variables (unlike the simple cases in this paper) so the homeostatic plateau will be a surface in a high dimensional space [46]. The challenge to mathematical modeling is to make physiologically based mathematical models of the underlying processes so that we can determine what these surfaces look like. Once we do this we can place known polymorphisms of key genes in their places on the surface as we did in Fig. 8. An individual's genetic makeup places him on the plateau, perhaps in the middle, perhaps near the edge. Being near the edge can be thought of as a "risk factor" for a particular disease, because an additional mutation or environmental shift can move the individual over the edge. Mutations and environmental variables can also reduce the size of the homeostatic region, thus releasing potentially deleterious cryptic genetic variation. The job of the medical practitioner would then be to recommend changes in the variables that the individual can control (diet, exercise, smoking, etc.) that will move the individual back towards the middle of the homeostatic plateau, or to suggest interventions that extend the homeostatic plateau. To do that, we need excellent mathematical models of how these behavior variables affect the homeostatic variables inside of cells.

Acknowledgments

This research was partially supported by NSF Grant EF-1038593 (H. Frederik Nijhout, Michael Reed), NSF agreement 0112050 through the Mathematical Biosciences Institute (Janet Best, Michael Reed), an NSF CAREER Award (Janet Best), the Alfred P. Sloan Foundation (Janet Best), and NIH Grant R01 ES019876 (D. Thomas).

References

[1] H.F. Nijhout, The nature of robustness in development, Bioessays 24 (2002) 553–563.
[2] A. Wagner, Robustness and Evolvability in Living Systems, Princeton University Press, Princeton, 2005.
[3] J.A.G.M. de Visser, J. Hermisson, G.P. Wagner, L.A. Meyers, H. Bagheri-Chaichian, J.L. Blanchard, L. Chao, J.M. Cheverud, S.F. Elena, W. Fontana, G. Gibson, T.F. Hansen, D. Krakauer, R.C. Lewontin, C. Ofria, S.H. Rice, G.v. Dassow, A. Wagner, M.C. Whitlock, Prespective: evolution and detection of genetic robustness, Evolution 57 (2003) 1959–1972.
[4] H.A. Woods, Evolution of homeostatic physiological systems, in: D.W. Whitman, T.N. Ananthakrishnan (Eds.), Phenotypic Plasticity of Insects, Mechanisms and Consequences, Science Publishers, Enfield, 2009, pp. 655–674.
[5] G. Gibson, I. Dworkin, Uncovering cryptic genetic variation, Nat. Rev. Genet. 5 (2004) 681–690.
[6] G. Gibson, Decanalization and the origin of complex disease, Nat. Rev. Genet. 10 (2009) 134–140.
[7] P.R. Morrison, Temperature regulation in three Central American mammals, J. Cell. Compar. Physiol. 27 (1946) 125–137.
[8] R. Carmel, D.W. Jacobsen, Homocysteine in Health and Disease, Cambridge Univ. Press, Cambridge, 2001.
[9] M.C. Reed, H.F. Nijhout, M.L. Neuhouser, J.F. Gregory, B. Shane, S.J. James, A. Boynton, C.M. Ulrich, A mathematical model gives insights into nutritional and genetic aspects of folate-mediated one-carbon metabolism, J. Nutr. 136 (2006) 2653–2661.
[10] H.F. Nijhout, M.C. Reed, D.F. Anderson, J.C. Mattingly, S.J. James, C.M. Ulrich, Long-range allosteric interactions between the folate and methionine cycles stabilize DNA methylation reaction rate, Epigenetics 1 (2006) 81–87.
[11] H.F. Nijhout, M. Reed, S.-L. Lam, B. Shane, J. Gregory, C. Ulrich, In silico experimentation with a model of hepatic mitochondrial folate metabolism, Theor. Biol. Med. Modell. 3 (2006) 40.
[12] K.A. Haijar, Homocysteine and hemostasis, in: R. Carmel, D.W. Jacobsen (Eds.), Homocysteine in Health and Disease, Cambridge Univ. Press, Cambridge, 2001.
[13] K. Kalantar-Zadeh, G. Block, M.H. Humphreys, C.J. McAllister, J.D. Kopple, A low, rather than a high, total plasma homocysteine is an indicator of poor outcome in hemodialysis patients, J. Am. Soc. Nephrol. 15 (2004) 442–453.
[14] O. Yorbik, A. Sayal, C. Akay, D.I. Akbiyik, T. Sohmen, Investigation of antioxidant enzymes in children with autistic disorder, Prostagl. Leukotr. Ess. Fatty Acids 67 (2002) 341–343.
[15] E. Sbrana, A. Paladini, E. Bramanti, M.C. Spinetti, G. Raspi, Quantitation of reduced glutathione and cysteine in human immunodeficiency virus-infected patients, Electrophoresis 25 (2004) 1522–1529.
[16] M.A. Savageau, G. Jacknow, Feedforward inhibition in biosynthetic pathways: inhibition of the aminoacyl-tRNA synthetase by intermediates of the pathway, J. Theor. Biol. 77 (1979) 405–425.
[17] J. Kremkow, L. Perrinet, G. Masson, A. Aertsen, Functional consequences of correlated excitatory and inhibitory conductances in cortical networks, J. Comput. Neurosci. 28 (2010) 579–594.
[18] M. Patel, M. Reed, Stimulus encoding within the barn owl optic tectum using gamma oscillations vs. spike rate: a modeling approach, Network: Comput. Neural Syst. 24 (2013) 52–74.
[19] G.G. Turrigiano, S.B. Nelson, Homeostatic plasticity in the developing nervous system, Nat. Rev. Neurosci. 5 (2004) 97–107.
[20] D.R. F Irvine, The Auditory Brainstem, Springer-Verlag, New York, 1986.
[21] N. Golding, D. Robertson, D. Oertel, Recordings from slices indicate that octopus cells of the cochlear nucleus detect coincident firing of auditory nerve fibers with temporal precision, J. Neurosci. 15 (1995) 3138–3153.
[22] D. Oertel, R. Bal, S. Gardner, P. Smith, P. Joris, Detection of synchrony in the activity of auditory nerve fibers by octopus cells of the mammalian cochlear nucleus, Proc. Natl. Acad. Sci. USA 97 (2000) 11773–11779.
[23] I. Sgouralis, A. Layton, Control and modulation of fluid flow in the rat kidney, Bull. Math. Biol. 75 (2013) 2551–2574.
[24] J.P. Briggs, J. Schnermann, The tubuloglomerular feedback mechanism: functional and biochemical aspects, Annu. Rev. Physiol. 49 (1987) 251–273.
[25] R.A. Wise, Dopamine, learning and motivation, Nat. Rev. Neurosci. 5 (2004) 483–494.
[26] A. Graybiel, T. Aosaki, A. Flaherty, M. Kimura, The basal ganglia and adaptive motor control, Science 265 (1994) 1826–1831.
[27] R. Feldman, J. Meyer, L. Quenzer, Principles of Neuropharmacology, Sinauer Associates, Sunderland, MA, 1997.
[28] G. Di Chiara, V. Bassareo, S. Fenu, M.A. De Luca, L. Spina, C. Cadoni, E. Acquas, E. Carboni, V. Valentini, D. Lecca, Dopamine and drug addiction: the nucleus accumbens shell connection, Neuropharmacology 47 (supplement 1) (2004) 227–241.
[29] J. Jankovic, Tourette's syndrome, New Engl. J. Med. 345 (2001) 1184–1192.
[30] H. Bernheimer, W. Birkmayer, O. Hornykiewicz, K. Jellinger, F. Seitelberger, Brain dopamine and the syndromes of Parkinson and Huntington Clinical, morphological and neurochemical correlations, J. Neurol. Sci. 20 (1973) 415–455.
[31] L.S. Kegeles, A. Abi-Dargham, W.G. Frankle, R. Gil, T.B. Cooper, M. Slifstein, D.-R. Hwang, Y. Huang, S.N. Haber, M. Laruelle, Increased synaptic dopamine function in associative regions of the striatum in schizophrenia, Arch. Gen. Psychiat. 67 (2010) 231–239.
[32] R.R. Gainetdinov, S.R. Jones, F. Fumagalli, R.M. Wightman, M.G. Caron, Re-evaluation of the role of the dopamine transporter in dopamine system homeostasis, Brain Res. Rev. 26 (1998) 148–153.
[33] M.C. Reed, A. Lieb, H.F. Nijhout, The biological significance of substrate inhibition: a mechanism with diverse functions, Bioessays 32 (2010) 422–429.
[34] M.C. Reed, J. Best, H.F. Nijhout, Passive and active stabilization of dopamine in the striatum, Biosci. Hypotheses 2 (2009) 240–244.
[35] J.A. Best, H.F. Nijhout, M.C. Reed, Homeostatic mechanisms in dopamine synthesis and release: a mathematical model, Theor. Biol. Med. Modell. 6 (2009) 21.
[36] M. Royo, S.C. Daubner, P.F. Fitzpatrick, Effects of mutations in tyrosine hydroxylase associated with progressive dystonia on the activity and stability of the protein, Proteins: Struct. Funct. Bioinform. 58 (2005) 14–21.
[37] P.M. Knappskog, T. Flatmark, J. Mallet, B. Lüdecke, K. Bartholomé, Recessively inherited L-DOPA-responsive dystonia caused by a point mutation (Q381K) in the tyrosine hydroxylase gene, Hum. Mol. Genet. 4 (1995) 1209–1212.
[38] G.M. Miller, B.K. Madras, Polymorphisms in the 3′-untranslated region of human and monkey dopamine transporter genes affect reporter gene expression, Mol. Psychiat. 7 (2002) 44–55.
[39] M.K. Hahn, M.S. Mazei-Robison, R.D. Blakely, Single nucleotide polymorphisms in the human norepinephrine transporter gene affect expression, trafficking, antidepressant interaction, and protein kinase C regulation, Mol. Pharmacol. 68 (2005) 457–466.
[40] R. De La Fuente-Fernández, J.-Q. Lu, V. Sossi, S. Jivan, M. Schulzer, J.E. Holden, C.S. Lee, T.J. Ruth, D.B. Calne, A.J. Stoessl, Biochemical variations in the synaptic level of dopamine precede motor fluctuations in Parkinson's disease: PET evidence of increased dopamine turnover, Ann. Neurol. 49 (2001) 298–303.
[41] J.Y. Chen, E.A. Wang, C. Cepeda, M.S. Levine, Dopamine imbalance in Huntington's Disease: a mechanism for the lack of behavioral flexibility, Front. Neurosci. 7 (2013).
[42] H.F. Nijhout, M.C. Reed, Homeostasis and dynamic stability of the phenotype link robustness and plasticity, Int. Comp. Biol. (2014) 1–12.
[43] P.K. Carmines, K. Ohishi, H. Ikenaga, Functional impairment of renal afferent arteriolar voltage-gated calcium channels in rats with diabetes mellitus, J. Clin. Invest. 98 (1996) 2564–2571.
[44] I. Sgouralis, A. Layton, Theoretical assessment of renal autoregulatory mechanisms, Am. J. Renal Physiol. 306 (2014) F1357–F1371.
[45] H.F. Nijhout, M.C. Reed, S.-L. Lam, J.F. Gregory, B. Shane, C.M. Ulrich, A day in the life of cell metabolism, J. Biol. Theory 2 (2008) 2124–2127.
[46] E.O. Voit, A systems-theoretical framework for health and disease: inflammation and preconditioning from an abstract modeling point of view, Math. Biosci. 217 (2009) 11–18.