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Homeostasis despite instability

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ABSTRACT

We have shown previously that different homeostatic mechanisms in biochemistry create input-output curves with a "chair" shape. At equilibrium, for intermediate values of a parameter (often an input), a variable, Z, changes very little (the homeostatic plateau), but for low and high values of the parameter, Z changes rapidly (escape from homeostasis). In all cases previously studied, the steady state was stable for each value of the input parameter. Here we show that, for the feedback inhibition motif, stability may be lost through a Hopf bifurcation on the homeostatic plateau and then regained by another Hopf bifurcation. If the limit cycle oscillations are relatively small in the unstable interval, then the variable Z maintains homeostasis despite the instability. We show that the existence of an input interval in which there are oscillations, the length of the interval, and the size of the oscillations depend in interesting and complicated ways on the properties of the inhibition function, f, the length of the chain, and the size of a leakage parameter.

1. Introduction

Most human and animal physiological systems can function well in the face of gene polymorphisms and changes in the environment because of rich networks of regulatory mechanisms. This is true at all levels of organization, from gene networks, to cellular biochemistry, to tissue and organ properties, and to the behavior of the whole organism. In the simplest case, this is illustrated conceptually by the function $Z(I)$ in Fig. 1. The variable Z depends on I, which could represent an input, an environmental variable, or some other variable of the system. However, over a large range of I (between $H_1 = 6$ and $H_2 = 15$ in Fig. 1), the value of $Z(I)$ changes very little. The homeostatic region is the range of I where $Z(I)$ changes very little. Outside the homeostatic region the regulatory mechanisms fail and $Z(I)$ changes rapidly as I varies; we call this escape from homeostasis [1]. Overall the curve giving the dependence looks like a chair [2], and examples of such chair curves abound: body temperature as a function of environmental temperature [1]; liver homocysteine concentration as a function of methionine input [1]; afferent arterial flow in the kidney as a function of blood pressure [3]; cerebral blood flow as a function of cerebral blood pressure [4]. In studying metabolism, we have found that many different kinds of biochemical mechanisms can produce chair curves [5]. Golubitsky and Stewart have used singularity theory as an analytical tool to find nodes in networks that are homeostatic with respect to an input [6].

We have investigated [5] many different biochemical mechanisms that give rise to homeostasis where, typically, I is an input to the network. In all of these cases, the system had a unique stable equilibrium for each I. In this paper we show an entirely new phenomenon. The steady state of the system can lose its stability, yet the system still shows a homeostatic region and a chair curve. Consider the simple biochemical chain pictured in Fig. 2. The last element in the chain, X_n, inhibits the reaction that takes X_1 to X_2. This kind of feedback inhibition is one of the most common homeostatic mechanisms in biochemistry [5]. The homeostatic variable is X_n because as I increases, X_n tends to increase, which increases the inhibition by f, limiting how much X_n rises.

For $n = 4$ and an appropriate choice of the inhibitory function, f, the system shows the behavior indicated in Fig. 3. For I small, the equilibrium is stable and $X_4(I)$ increases linearly in I. At the value I_1 there is a Hopf bifurcation and the equilibrium becomes unstable but shows homeostasis (the red curve). Finally at I_2, the equilibrium becomes stable again and shortly thereafter $X_4(I)$ shows escape from homeostasis by rising linearly with I. For I in the interval (I_1, I_2), the system has a stable limit cycle; the green curves show the maximum and minimum values of $X_4(I, t)$ as $X(I, t)$ traverses the limit cycle for fixed I.

Consider biological experiments on this system where the experimenter chooses an input, I, and then measures X_4. When $I < I_1$, the measurements will cluster tightly about the stable equilibria on the blue curve. For $I_1 < I < I_2$, there will be more spread of the measured values because X_4 is changing in time because the dynamics has a limit cycle.

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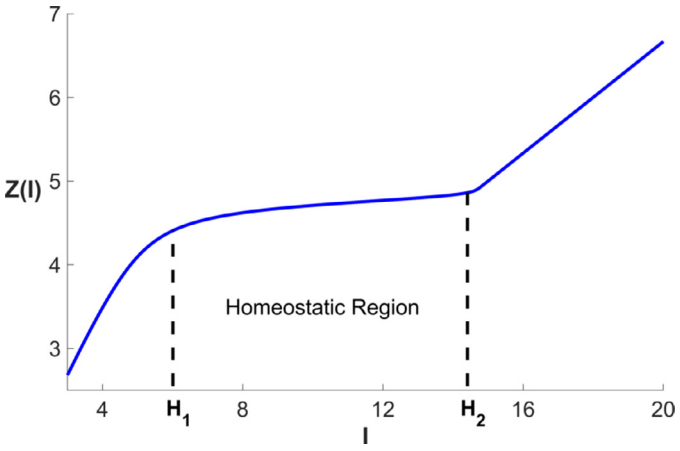

Fig. 1. A classic chair curve. The variable Z shows homeostasis and escape from homeostasis with respect to the variable I.

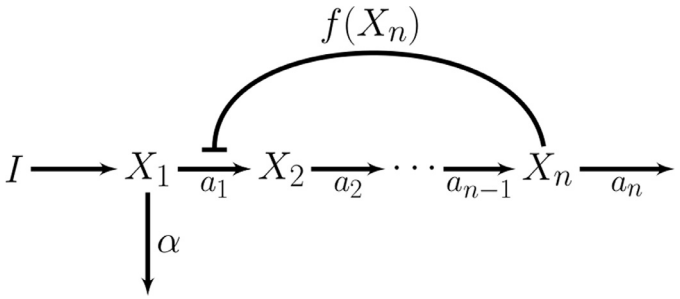

Fig. 2. A simple biochemical chain with feedback inhibition. The variable X_n inhibits the reaction that takes X_1 to X_2 via the function $f(X_n)$. I is the input to the chain.

The spread of the measured values of X_4 will be between the upper and lower green curves (except for measurement error). When $I > I_2$, the measurements will again cluster tightly about the stable equilibria on the blue curve. The experimenter may not know of the existence of the limit cycles, but will notice that there is more spread of the measured values of X_4 when $I_1 < I < I_2$. Since the upper and lower green curves are close to each other, the total set of measured values of X_4, over a wide range of choices of I, will show the same general shape of a chair curve with a homeostatic region in the middle. This is what we mean by "homeostasis despite instability."

In Section 2, we investigate how the phenomenon of homeostasis despite instability depends on network length, n, properties of the feedback function, f, and the value of α. In Section 3, we assume that f has a special form depending on only three parameters, the slope of f, the minimum of f, and the location of the region with constant negative slope. We present numerical calculations that show how the size of the unstable region and the amplitude of the limit cycles depend on these three parameters. In the Discussion, we explain that another homeostatic motif, the parallel inhibition motif [5], shows similar behavior, so homeostasis despite instability is not limited to the feedback inhibition motif.

2. Dependence of stability on network length

Throughout this section we make the following assumptions about f:

$$f \text{ is differentiable, } f > 0, \text{ and } f' \le 0. \tag{1}$$

We assume $f > 0$ so that the backwards reaction of $X_2 \to X_1$ does not occur and the forward reaction of $X_1 \to X_2$ always occurs at some rate. The assumption that $f' \le 0$ is made so that X_n inhibits the production of X_2 from X_1. Additionally, we assume $a_j > 0$ for each j. Other hypotheses will be introduced as appropriate. Let $x_i(t)$ denote the concentration of X_i at time t. Each differential equation expresses that the rate of change of the variable is the rate at which it is made minus the rate at which it is consumed. We assume mass action kinetics for all reactions except for the rate from X_1 to X_2 that depends on inhibition from X_n expressed through f. The dynamics are given by

$$\begin{aligned}
\dot{x}_1 &= I - (a_1 f(x_n) + \alpha)x_1 \\
\dot{x}_2 &= a_1 f(x_n)x_1 - a_2 x_2 \\
\dot{x}_3 &= a_2 x_2 - a_3 x_3 \\
&\vdots \\
\dot{x}_n &= a_{n-1}x_{n-1} - a_n x_n
\end{aligned}$$

where dot indicates a derivative in t. When $\alpha = a_2$, $\dot{x}_1 + \dot{x}_2 = I - a_2(x_1 + x_2)$ so that as $t \to \infty$, $x_1 + x_2 \to I/a_2$. This allows us to reduce the dimension of the steady state Jacobian by 1 and to significantly simplify the analysis. We are interested in how n and the properties of f affect the stability of equilibrium solutions to this system. For $n = 2$, 3, and4, we are able to characterize when an equilibrium is stable, and we can do the same for $n = 5$ if $\alpha = 1$. For general n, we give a necessary condition for instability and a sufficient condition for instability, but neither is necessary and sufficient.

Using the equations above, it is easy to see that the steady state solutions satisfy:

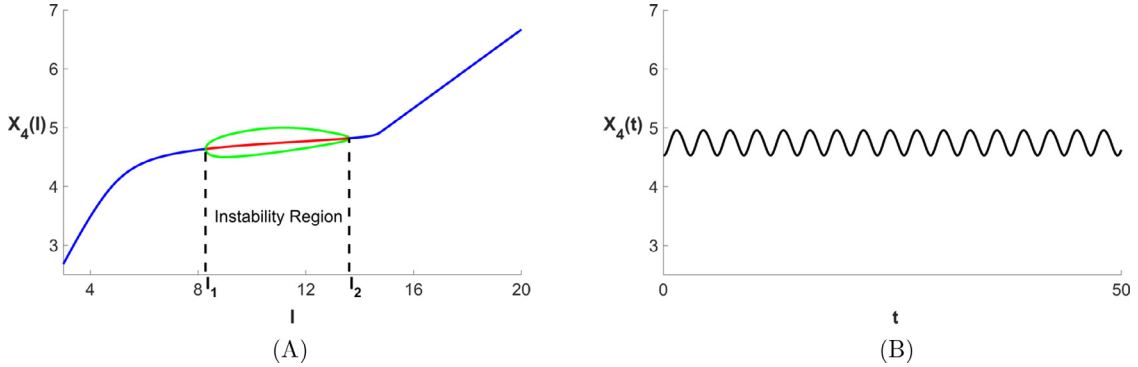

Fig. 3. Homeostasis despite instability. In the feedback chain in Fig. 2, the equilibrium becomes unstable for I in the interval (I_1, I_2) for an appropriate choice of the feedback function f. We chose $n = 4$, $\alpha = 1$, $a_j = 1$ for each j, and $f(x) = 10e^{-1/(5-x)+1/5}\Theta(5-x) + 1/2$, where $\Theta(x)$ is the Heaviside step function. In Panel A, the blue and red curves show the values of $X_4(I)$ at the stable and unstable equilibria, respectively. The green curves show the maximum and minimum values of X_4 as the dynamics traverses the limit cycle for fixed I. Since the green curves are close to each other, experimental measurements (see text) will follow the shape of the curve of equilibria despite the instability. In Panel B we show the time course of the oscillations in X_4 for $I = 10$, where the maximum amplitude oscillations are obtained. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)