J. theor. Biol. (2000) **206,** 211–220
doi:10.1006/jtbi.2000.2118, available online at http://www.idealibrary.com on IDEAL®

Integral Rein Control in Physiology II: a General Model

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(*Received on* 12 *November* 1998, *Accepted in revised form on* 1 *June* 2000)

We generalize the principle of integral rein control to include other systems which partition in such a way that the equilibrium values of some variables are not dependent on the equations governing those variables. Instead, they are determined by the dynamics of other, "regulator" variables. We improve our earlier model for the control of glucose by insulin and glucagon by relaxing the condition necessary for it to operate. The two hormones do not have to be inhibited in the same way; they need only respond to the same combination of their concentrations. We also present a model for the control of ionized calcium by PTH and calcitonin and suggest that the role of chromogranin A may be to stabilize an otherwise unstable system.

Introduction

In previous papers (Koeslag *et al*., 1997; Saunders *et al*., 1999; henceforth (I) and (II), respectively), we introduced a principle which we called integral rein control (IRC). This combines the zero steady-state error of integral control with the stability against substantial perturbations in either direction which is characteristic of rein control (Clynes, 1969). An important feature is that the set point is fixed dynamically rather than by an external reference.

We used this principle to derive a model for the control of blood glucose by insulin and glucagon. Our model explains how glucose can be so closely and reliably regulated. It also accounts for some of the important differences between the two types of diabetes, and in particular why glycaemic control is much easier in Type II diabetes than in Type I diabetes.

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The most restrictive property of the original model was that it assumed a strong symmetry between the hormones: the two had to be inhibited by themselves and each other in the same way. In this paper, we present a more general IRC model which allows us to weaken this assumption. It requires only that the hormones respond to the same function of the hormone concentrations; it allows the responses themselves to be quite different.

The new model also includes the case in which there are more substances involved in regulation and/or more than one substance being regulated. We use it to model the control of calcium ion concentration, based on the hypothesis (Koeslag *et al*., 1998) that in addition to PTH and calcitonin, a chromogranin-derived peptide is involved. Our results suggest that when there is little or no removal of a regulated substance by dilution or demand, a system with four components is more likely to be stable than is a system with only three.

0022–5193/00/180211 + 10 $35.00/0

The Model

Consider a system which may be very large and complex, but can be described by a set of n state variables $x_1, \ldots, x_n$ where n is finite. We suppose that there is also a set $u_1, \ldots, u_m$ of external variables, which influence the system but are not influenced by it. In our earlier model of glucose control, for example, there are three state variables, the concentrations of glucose, glucagon and insulin, and two external variables, the rate of input of glucose from the gut and from the liver, and the demand for glucose from the brain, muscles and other tissues. We also suppose that the system can be described by a set of n first-order ordinary differential equations

$$\frac{dx_i}{dt} = f_i(x_1, \ldots, x_n; u_1, \ldots, u_m), \quad i = 1, \ldots, n. \qquad (1)$$

Now, in general, we would not expect that each of these n equations will involve all n state variables. In particular, it may be that there are k state variables, which we may take to be $x_1, x_2, \ldots, x_k$, such that the equations

$$f_i(x_1, \ldots, x_n; \mathbf{u}) = 0, \quad i = 1, 2, \ldots, k, \qquad (2)$$

involve only k functions of the state variables; we denote these by $y_i(x_1, \ldots, x_n)$. (Here $\mathbf{u}$ is an abbreviation for $u_1, \ldots, u_m$.) Then we can obtain the steady-state values of the k functions y_i from the k equations (2) alone; we do not require the full system (1).

(Note that this does not mean that the right-hand sides (r.h.s.) of the first k differential equations must involve only the k functions y_i. In fact, while we shall suppose this to be the case in the examples in the rest of this paper, the argument requires only the somewhat weaker condition that the first k functions $f_i(\mathbf{x}, \mathbf{u})$ must factor

$$f_i(x_1, \ldots, x_n; \mathbf{u}) = g_i(y_1, \ldots, y_k; \mathbf{u})\, h_i(x_1, \ldots, x_n; \mathbf{u}), \quad i = 1, 2, \ldots, k \qquad (2a)$$

and that at equilibrium it is the g_i that vanish, not the h_i.)

Suppose that we are modelling a large, complex system that can be described by a system of n ordinary differential equations, where n may be a large number. It may well be that we cannot write down all the equations, and we may not even know how large n is. Yet providing there is a set of k equations that satisfy the condition described above, we can obtain the steady-state values of a set of k variables y_i.

In particular, if no external variables are involved in eqns (2), then the steady state is independent of the values of the external variables; this is a generalization of the case of integral rein control described in (II). Consistent with this, we shall refer to the x_i ($i = 1, \ldots, k$) as the *regulator* variables and the y_i ($i = 1, \ldots, k$) as the *regulated* variables.

Of course, it may be that the system simply divides completely into two parts, with the first k variables independent of the rest. This is, however, the trivial case; in general, the regulated variables y_i will not be merely functions of the k regulator variables x_i. It may well be that one of the regulated variables is simply one of the remaining variables x_i (i.e. with $i > k$), and in that case we can determine the steady-state value of a variable for which we may not even know the form of corresponding differential equation. This means that we may not have to know the differential equation that describes the behaviour of the variable of the most interest to us in order to find its steady-state value.

This may sound surprising, but it is only a generalization of what happens in a simple control system. The transient behaviour of the variable being controlled may be influenced by many different factors, but the steady-state value is determined by the setting of the controller.

Integral Rein Control: the Case $k = 2$

For this paper, we concentrate on the case $k = 2$, in which there are two regulator variables and, accordingly, two regulated variables. This is integral rein control as described in our previous papers, although here we provide a more general model. The case $k = 1$ is ordinary integral control, and $k \geqslant 3$ is more complicated than we expect to observe in a single physiological regulatory system, though it may be relevant in ecology and other contexts. We use much the same parameter values as in (II), partly for ease of

comparison, and partly because we have already verified that these are of the right orders of magnitude.

GLUCOSE REGULATION

In (II) we proposed the following equations as a model for the control of blood glucose by glucagon and insulin:

$$\frac{dA}{dt} = A(\phi(G)h_1(A, B) - D_{(A)}), \tag{3}$$

$$\frac{dB}{dt} = B(\psi(G)h_2(A, B) - D_{(B)}), \tag{4}$$

$$\frac{dG}{dt} = I + \alpha(A, G) - \beta(B, G) - \gamma(R, G). \tag{5}$$

Here A, B, G are the concentrations of glucagon, insulin and glucose, respectively, I is the rate of input of glucose to the system and R stands for the demand, and $D_{(A)}$ and $D_{(B)}$ are constants. The functions $\alpha(A, G)$, $\beta(B, G)$ and $\gamma(R, G)$ are increasing functions of both their arguments, and $h_1(A, B)$ and $h_2(A, B)$ are decreasing functions of both their arguments. Finally, $\phi(G)$ is a decreasing function of G and $\psi(G)$ is an increasing function of G.

The main result of (II) was that if $h_1(A, B) = h_2(A, B)$ then there is a steady state in which $\tilde{G}$, the equilibrium value of G, is independent of I and R. If, without loss, we set $D_{(A)} = D_{(B)} = D$, then $\tilde{G}$ is the value of G at which the curves of $\phi(G)$ and $\psi(G)$ intersect.

For the particular case of glucose control, it is reasonable to assume that the condition $h_1(A, B) = h_2(A, B)$ holds, on account of the direct link between the α-cells that produce glucagon and the β-cells that produce insulin [see (I)]. The model is also structurally stable; if the inhibition functions are approximately equal, then $\tilde{G}$ is approximately constant, which is sufficient. It is, however, harder to justify this condition in other cases, where the hormones are produced in quite different parts of the body.

We can now weaken the condition considerably by taking advantage of the result of the previous section. We do not have to require that the two inhibition functions have to be the same. They need only depend on the same combination of the hormone concentrations:

$$h_1(A, B) = h_1(f(A, B)),$$

$$h_2(A, B) = h_2(f(A, B)) \tag{6}$$

We can now set the time derivatives equal to zero in eqns (3) and (4) and solve the resulting algebraic equations to obtain the steady-state values of the regulated variables G and $f(A, B)$; in the notation of the previous section these are the variables y_1 and y_2. Finally, we can use eqn (5) to obtain the steady-state values $\tilde{A}$ and $\tilde{B}$ separately.

Thus, the α- and β-cells do not have to be inhibited in the same or even similar ways. We may say that they have to read the concentrations in the same ways, but how they respond may be quite different. This includes the possibility (cf. I) that it is only the β-cells that respond directly to conditions and that the α-cells produce glucagon or not in accordance with signals from the β-cells.

As an example, we have carried out calculations based on the following model:

$$\frac{dA}{dt} = A(\phi(G)(K - A - B) - D), \tag{7}$$

$$\frac{dB}{dt} = B\left(\psi(G)\frac{\mu}{1 + (A + B)^2} - D\right), \tag{8}$$

$$\frac{dG}{dt} = I + \alpha A - \beta B - RG. \tag{9}$$

Here the two regulator variables are A and B and the two regulated variables are G and $A + B$.

To facilitate comparison with our results in (II), we used the same values $K = 6$, $\alpha = \beta = 2.93$, $D = 0.1$ and set $\mu = 4.95$ to make the initial values the same as in the earlier example. The results for the case of varying demand I are illustrated in Fig. 1; the agreement in the case of varying input R is even closer. We have computed the eigenvalues of the stability matrix as either R or I varies, and these too are very much the same as those obtained in (II). The only

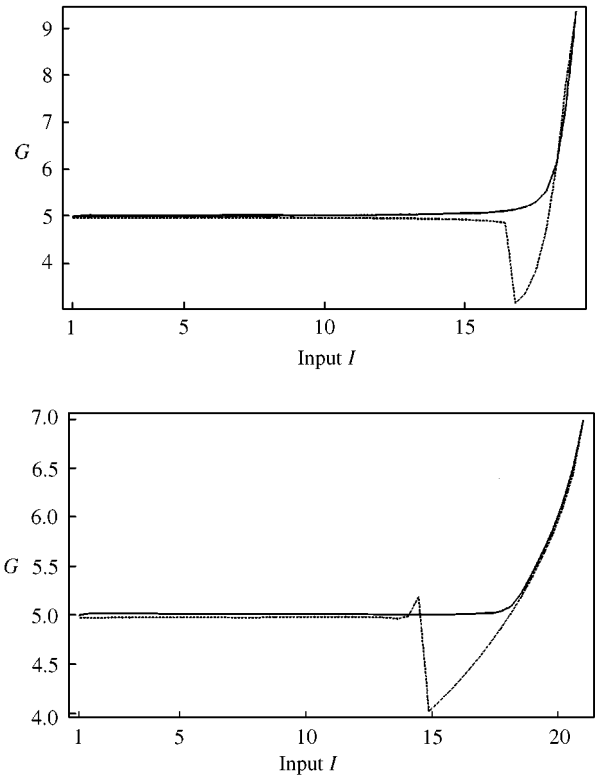

FIG. 1. Variation of blood glucose G as the input I is increased to 20 times its nominal value (——) and then back (- - - - -) using the relation $I = 1 + 0.01t$, which corresponds to doubling in about half an hour. The curves in (a) were computed using the same inhibition function $h(A, B)$ [as in (II)], whereas those in (b) were computed using different inhibition functions [eqns (7) and (8)].

significant difference is that for relatively large I the magnitude of the least negative eigenvalue is somewhat less, which is why there is a small oscillation in the return trajectory in Fig. 1(b).

Ca^{2+} REGULATION

The concentration of calcium ions in the blood is closely regulated, at about 1.2 mmol l^{-1}. This is chiefly accomplished by two hormones, the parathyroid hormone (PTH), which is secreted from the parathyroid gland and acts to increase the concentration of Ca^{2+}, and calcitonin, which is secreted from the C cells of thyroid gland and which acts to decrease the concentration of Ca^{2+}. The rate of secretion of PTH decreases and that of calcitonin increases, both almost linearly, with increasing plasma ionized calcium levels.

The situation is somewhat similar to that of glucose control, but there are two significant differences. First, whereas the α- and β-cells are located together in the islets of Langerhans [and indeed we have suggested (Koeslag *et al.*, 1997) that syncytial groups can switch between the two roles], the parathyroid glands are anatomically remote from the thyroid gland. Second, a chromogranin-derived peptide (possibly $CgA_{(1-40)}$: we shall refer to it simply as CgA) is co-stored and co-secreted with both PTH and calcitonin and inhibits the secretion of both (Cohn *et al.*, 1984, 1995; Deftos *et al.*, 1990; Fasciotto *et al.*, 1990; Drees *et al.*, 1991, 1994; Zhang *et al.*, 1994).

We have therefore proposed (Koeslag *et al.*, 1999) that what matters in calcium ion regulation is not the mutual and self-inhibition of the two hormones but rather the separate inhibition of each of them by CgA. Like our model for glucose regulation, this is a system with $k = 2$, but in this case the regulated variables are distinct from the regulator variables.

We illustrate our hypothesis with the following model:

$$\frac{dA}{dt} = A(\phi(C)h_1(H) - D), \tag{10}$$

$$\frac{dB}{dt} = B(\psi(C)h_2(H) - D), \tag{11}$$

$$\frac{dC}{dt} = I + \alpha(A, C) - \beta(B, C) - D_C C, \tag{12}$$

$$\frac{dH}{dt} = \mu(A\phi(C)h_1(H), B\psi(C)h_2(H)) - DH. \tag{13}$$

Here A, B, C and H are the concentrations of PTH, calcitonin, Ca^{2+} and CgA, respectively. The function $\phi(C)$ is an increasing function of C, whereas $\psi(C)$ is a decreasing function of C. The functions $\alpha(A, C)$ and $\beta(B, C)$ are increasing functions of both arguments, and $h_1(H)$ and $h_2(H)$ are decreasing functions of H. The input of Ca^{2+} from the gut is denoted by I, and D and D_C are constants. We would expect D_C to be much smaller than D, as there is relatively little loss of ionized calcium from the blood other than that

mediated by the hormones. Equation (13) simply states that the rate of secretion of CgA is a function of the rates of secretion of the two hormones; in modelling we shall take it to be a (possibly weighted) sum of the rates. For simplicity, we have assumed that the rate of secretion of CgA is not affected by any variables external to the system represented by eqns (10)–(13), but the situation is not materially altered if it is.

Equations (10) and (11) include no mutual or self-inhibition by the two hormones. This does not mean that we are assuming that no such inhibition ever occurs, only that within the range in which the regulation operates, the inhibitory effect of CgA is much greater than that of the hormones themselves.

Note that on this model, the concentration of CgA remains constant. This is not strictly essential to the hypothesis, because if PTH and calcitonin are inhibited by two substances, CgA and something else, then only some function of the two latter concentrations would have to be constant. Nevertheless, it does suggest the apparently paradoxical idea that if the CgA concentration is found to be constant, this actually supports the hypothesis that CgA is involved in the regulation of ionized calcium. Intuitively, we would expect substances involved in regulation to vary, as of course the hormone concentrations do.

To illustrate the model we have taken

$$h_1(H) = h_2(H) = K - H,$$

but this is only for simplicity; the principle does not require that the functions be the same. As in (II) we used simple functions for $\phi(C)$ and $\psi(C)$:

$$\phi(C) = \begin{cases} 1, & C < 0.2, \\ 1 - (C - 0.2)^2/4, & 0.2 < C < 2.2, \\ 0, & C > 2.2, \end{cases} \tag{14}$$

$$\phi(C) = \begin{cases} 0, & C < 0.2, \\ 1 - (C - 2.2)^2/4, & 0.2 < C < 2.2, \\ 1, & C > 2.2. \end{cases}$$

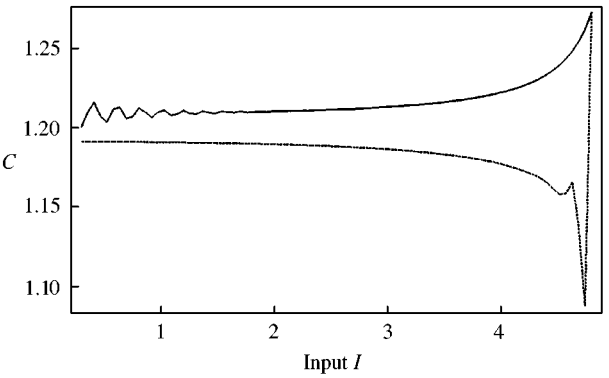

FIG. 2. Variation of ionized calcium C as the input I is increased to 18 times its nominal value (——) and then back (- - - - -).

We took $\alpha(A, C) = \alpha A$ and $\beta(B, C) = \beta B$ and we used the following values for the parameters:

$$\alpha = \beta = 0.87, \quad D = 0.1, \quad D_C = 0.01,$$

$$K = 6, \quad \mu = 1.$$

The results are illustrated in Fig. 2, and are clearly much the same as for either glucose model.

An important property of a three-component IRC system is that if one of the regulator variables is absent, there is no longer a set point. There is in general still an equilibrium value for the regulated variable, but it is no longer independent of the external variables and it is typically quite different from the set point that exists under normal conditions. This can readily be seen by considering eqns (7)–(9). If, for example, we set $B \equiv 0$, the steady-state equations become

$$\phi(G)(K - A) = D, \quad I + \alpha A - RG = 0 \tag{15}$$

and $\tilde{G}$, the steady-state value of G, now clearly depends on both I and R. What is more, for the "nominal" values of I and R (i.e. the input and demand levels for an individual who is resting and has not recently eaten) $\tilde{G}$ will be considerably higher than the set point [see (II)]. This happens because under normal conditions, G is maintained at the set point by a balance between the action of A and that of B even when I and R have their nominal values. (If B is not present, A will push G to a higher level.) As we have previously

pointed out, this can explain why Type I diabetes is so difficult to manage.

A similar effect can be observed in a four-component IRC system. If, for example, in eqns (10)–(13) we set $B \equiv 0$, then the three remaining steady-state equations no longer have $\tilde{C} = \text{const.}$ as a solution. There is, however, an important extra feature. At steady state, and with $B \equiv 0$, eqn (10) becomes

$$\phi(\tilde{C})\, h_1(\tilde{H}) - D = 0. \tag{16}$$

We note that $\tilde{C}$ depends only on $\tilde{H}$, not on $\tilde{A}$. Consequently, if the CgA concentration could somehow be clamped at the normal value, PTH would regulate the calcium ion to its normal concentration as well.

If one of the regulators in a three-component IRC system fails, the regulated variable must be controlled by direct intervention. This may be difficult to do with sufficient precision, as is the case in diabetes. A four-component system offers an additional possibility, however. Using our model of calcium ion concentration as an example, it implies we need clamp only either the CgA or the calcium ion concentrations to keep both at their proper levels. If there are physiological reasons why both should be more or less constant, that clearly makes treatment easier, since a single intervention will do for both. Suppose, however, that the precise concentration of CgA turns out not to be especially important. What the model then suggests is that clamping CgA might still be an appropriate intervention because it would be an indirect but effective way of keeping the calcium ion concentration at its proper level (see Koeslag *et al.*, 1999).

The indications that this might work in practice would be first that the CgA concentration is normally approximately constant and, second, that it changes when the calcium ion concentration changes, and similarly, of course, for other pairs of variables.

The control of blood calcium ion concentration is mediated by the calcium-sensing receptor (CASR). This is found both in the parathyroid, where it affects the release of PTH and also along the kidney tubule, where it affects the rate of excretion of calcium by the kidney. Mutations can cause the CASR to be less active, which can raise the set point for Ca^{2+}, i.e. produce hypercalcaemia, or to become more active, which lowers the set point and so causes hypocalcaemia (Brown & Herbert, 1997; Pearce & Thakker, 1997; see also Cole *et al.*, 1999.)

We can incorporate this into the model, representing changes in the activity of CASR by changes in the function $\phi(C)$ in eqn (10). We now verify that the set point in the model moves in the right direction; this is obvious for a system with three components but has to be checked when there are four.

Suppose that the activity is reduced. Then for any given value of C, the rate of secretion of PTH will be greater than normal, and we can represent this by replacing eqn (10) by

$$\frac{\mathrm{d}A}{\mathrm{d}t} = A(\hat{\phi}(C)\, h_1(H) - D), \tag{10a}$$

where $\hat{\phi}(C) > \phi(C)$ for all C, or at any rate for all C within the range that concerns us.

Let the equilibrium concentrations of Ca^{2+} and CgA be $(\tilde{C}, \tilde{H})$ in the case of normal CASR activity and $(\tilde{C}', \tilde{H}')$ in the case of reduced CASR activity. Then from eqns (10), (10a) and (11), we have

$$\phi(\tilde{C})\, h_1(\tilde{H}) = D, \tag{17}$$

$$\psi(\tilde{C})\, h_2(\tilde{H}) = D, \tag{18}$$

$$\hat{\phi}(\tilde{C}')\, h_1(\tilde{H}') = D, \tag{19}$$

$$\psi(\tilde{C}')\, h_2(\tilde{H}') = D. \tag{20}$$

To show that $\tilde{C}' > \tilde{C}$ we suppose the opposite, that $\tilde{C} > \tilde{C}'$. If that is so, then $\psi(\tilde{C}) > \psi(\tilde{C}')$, and then from eqns (18) and (20) it follows that $h_2(\tilde{H}) < h_2(\tilde{H}')$. Because h_2 is a decreasing function of H this implies that $\tilde{H} > \tilde{H}'$ and this in turn implies that $h_1(\tilde{H}) < h_1(\tilde{H}')$. It now follows from eqns (17) and (19) that $\phi(\tilde{C}) > \hat{\phi}(\tilde{C}')$, and since $\hat{\phi}(\tilde{C}') > \phi(\tilde{C}')$ by the definition of $\hat{\phi}$, we have that $\phi(\tilde{C}) > \phi(\tilde{C}')$ and so $\tilde{C} < \tilde{C}'$. This contradicts our original assumption, and so we conclude that $\tilde{C}' > \tilde{C}$, i.e. that reduced CASR activity in the parathyroid should lead to hypercalcaemia.

A similar calculation shows that increased CASR activity in the parathyroid should lead to hypoglycaemia. We can also show that in both cases the set point for CgA will move in the same direction as that for Ca^{2+}.

We have not included the effect of CASR on the action of the kidneys because in the model this would appear as a term in eqn (12), and this is not involved in determining the equilibrium value of the Ca^{2+} concentration, C. This is consistent with a general principle of integral rein control that the set point depends only on what happens in the controllers.

Stability

When a system is under integral rein control, the equilibrium values of the regulated variables do not depend on the external variables. If, therefore, the external variables are changed slowly, the regulated variables will not change at all so long as both of the regulator variables are present. In the case of calcium ions, for example, the steady-state analysis predicts that as the input is increased, the concentration of PTH should fall and that of calcitonin should increase, but the calcium ion concentration should remain constant until the PTH has fallen to zero. Only then should the calcium ion concentration start to rise.

In practice, of course, external variables such as the input do not change arbitrarily slowly. We have therefore solved the differential equations (10)–(13) numerically. We find (Fig. 2) that the calcium ion concentration begins to rise almost at once, though not by much, but that the rise becomes steeper at an input of about $I = 4$. In this model, and with the given parameter values, the PTH concentration falls to zero at $I = 5.11$.

We expect both phenomena should be observed in real systems. In particular, the relatively sharp rise before the PTH concentration has fallen to zero occurs because $I = 5.11$ is a bifurcation point for the system. The equilibrium with $C = \text{const.}$ becomes unstable there, and this means that the system will become less stable as I approaches this value. In the case of step changes in I, this will be observed as larger over- and undershoots; in the case of smooth changes, the calcium ion concentration will be significantly above the equilibrium level when I is increasing and below it when I is decreasing.

This feature does not depend on the details of the model: in general, integral rein control can operate only within a certain range of the variables, and as we approach the boundary of this range, the system will take longer to recover from perturbations. By the same token, it will also show some transient response to all but the very slowest changes in the external variables.

That the system does not exhibit a precise return to $C = 1.2$ when the input is reduced (Fig. 2; broken line) is also a transient phenomenon. If I is maintained at any value between its nominal value and the bifurcation point (in the model these are 0.3 and 5.11, respectively), the variables A, B, C and H will all return to their equilibrium values, which in the case of C is 1.2 for all values of I in that range.

In (II) we analysed the stability of the glucose model with identical inhibition functions $h_i(A, B)$. We found that when I and R had their nominal values, the eigenvalues of the stability matrix were

$$\lambda_1 = -3A/2,$$

$$\lambda_{2,3} = \tfrac{1}{2}[-R \pm \sqrt{R^2 - 16AD(\alpha+\beta)/15}]. \quad (21)$$

With the given values of the parameters the numerical values are -4.40, $-0.10 \pm 0.67i$. The form of the expression for λ_2, λ_3 indicates that as R decreases, the system will become less stable. If, for example, we leave all the other parameters the same and set $R = 0$, the eigenvalues are -4.40, $-0.0002 \pm 0.68i$. (The real parts of the last two are not quite zero because keeping the other parameters unaltered means that A and B are not equal when I and R have their nominal values and so eqn (15) does not apply.)

If we repeat the calculations using $h_2 = \mu/(1 + (A + B)^2)$ and the parameters given above, then we cannot derive a simple analytical expression for the eigenvalues, but we can readily determine them numerically: they are $(-2.30, -0.10 \pm 0.67i)$ for $R = 0.2$ and $(-2.18, 0.005 \pm 0.693i)$ for $R = 0$, so the general behaviour is very much the same.

Thus, the robustness of the regulation is strongly dependent on R, which represents the rate at which glucose is removed from the blood to supply energy to the muscles, i.e. other than by the action of the two hormones. Intuitively, this seems right; we would expect that other things being equal, a system with a large flux should be more stable.

The coefficient of C in eqn (12) is taken to be very small because comparatively little calcium is removed from the blood stream in an analogous way. Nevertheless, the eigenvalues of the stability matrix for the system (10)–(13) are, with the above values of the parameters, $(-0.1,\ -0.1 \pm 0.71i,\ -4.40)$, so the resilience, as measured by the least negative real part, is precisely the same as in the three component model with $R = 0.2$. This remains the case even if we take $D_C = 0$. Dilution, or its equivalent, generally has a stabilising effect (as can be seen from the fact that it implies a negative entry on the main diagonal of the stability matrix), and it appears that where this effect is weak, a four-component system is more likely to be stable.

Hierarchical Systems

Systems theorists have recognized for a long time that large complex systems are often organized hierarchically (see, e.g. Simon, 1962), by which they mean that the system is partitioned into subsystems in such a way that components within a subsystem interact directly only with other components within the same subsystem. Interaction between elements of different subsystems occurs only indirectly through interactions at the level of subsystems. This is what we observe here. The regulator variables, the hormones, interact with the rest of the system (not included in the model) only indirectly, through their effect on the regulated variables, i.e. glucose or calcium ions.

We also expect that a similar phenomenon should be observed in other complex systems, though possibly with many more variables involved and without the precise regulation we observe in some physiological systems. For example, in an ecosystem the regulated variables could include some common resource, and the regulators could be the populations of species that depend on the resource and also compete for space, like the daisies in the Daisyworld model (Watson & Lovelock, 1983). The weighted sum of the populations would almost certainly be one of the transformed variables, as it is in Daisyworld (Saunders, 1994). In such a case, we would not expect the level of the resource actually to remain constant, because all species would be acted upon by external variables. On the other hand, if the system partitioned in the way we are suggesting, the effect would be that even if the resource was directly affected by the environmental variables, its level would depend on the way that those variables acted on the other species, not on the resource itself.

Where this sort of partitioning occurs, it can allow us to gain information about variables, perhaps the ones we are most interested in, for which we are unable to write down the relevant equations. This is especially likely to be the case with important variables which interact directly with many others. For example, we know that the release of glucose into the blood can be stimulated in a number of ways, and that eqn (5) is therefore an oversimplification. Fortunately, we do not rely on this equation either for the inference that the glucose concentration will remain constant over a wide range of parameter values or for determining what this constant level will be.

One of the problems encountered in the study of complexity is that systems of coupled differential equations must be solved as a whole; the variables of interest to us can only be separated out afterwards. Like the splitting lemma of catastrophe theory, the partitioning described in this paper can make it possible to get round this difficulty. There is no shortcut available if we want a full solution, but we may be able to gain useful information with much less effort.

Conclusions

There are two distinct forms of integral rein control. In one, the system has only three components and the two regulators must "read" the concentrations of the regulated variables in the same way, though they may respond quite differently. In the other, there is a second regulated

variable and then the regulators must not significantly inhibit themselves or each other near the steady state. When the variable to be regulated is not subject to dilution or removed from the system in some other way roughly proportional to its own concentration, a system with four components is more likely to be stable than one with only three.

We expect that integral rein control should be common in physiological systems, especially since integral control in general arises naturally where regulation involves chemical rate equations. Because the concentrations of the regulators are themselves specified by first-order differential equations, they automatically appear in the equations for the regulated variables as integrals.

The most obvious sign of integral rein control is that a system can maintain a quantity at a nearly constant level despite significant and sustained changes in other variables that affect it. The key point is not that the system is stable against short-term perturbations (though it is) but that it exhibits zero steady-state error: the equilibrium value of the regulated quantity remains the same even when the value of some important external variable (such as the rate of input of the quantity into the system) is altered to and remains at a value substantially above or below the expected one.

A second important characteristic is that the set point is fixed dynamically, not by comparison with some external reference. This is likely to make the fixed point constant over the lifetime of an individual organism and also the same for different organisms. It also means that damage to the control system will typically not just make the set point harder to maintain, it can destroy it altogether, as in Type I diabetes. This does not happen in Type II diabetes because the problem is not in the control system itself but in the response to the control. As we pointed out in (I) and (II), this is why Type I diabetes is so much more difficult to manage. It is not a question of bringing the system back to a set point; the problem is to maintain the glucose concentration at a level which, while it is still optimal for the patient, is no longer a natural equilibrium point of the system.

As we have seen, there are two distinct kinds of IRC systems, those with three components and those with four. Four-component systems have two separate variables that are held constant. It follows that a indication that a four-component IRC is in operation is that some variable is being held constant when there seems no obvious reason why it should be. Thus, for example, if our model of calcium ion control is correct, we would expect that the concentration of certain CgA species (those that are cosecreted into the blood with the two counterregulatory hormones) should be constant.

We would also expect that the concentration of those CgA species should alter if a failure of regulation causes the calcium ion concentration. In such cases, clamping the CgA concentration could be an alternative method of maintaining the calcium ion concentration at its optimum level.

More generally, our results suggest that it would be useful to identify substances whose concentration is approximately constant under normal conditions, whether this appears to be physiologically important or not. If any of them is observed to change when some regulatory system is impaired, then that substance may be the second variable of an IRC pair, and knowing this might allow a wider range of possible interventions.

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