

Integral Rein Control in Physiology

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Abstract

We propose that blood glucose is regulated by a principle which we call integral rein control, in which under most conditions both glucagon and insulin are produced and control is achieved by altering the balance between the two. Like other integral control systems, the mechanism achieves zero steady state error, which explains how the blood glucose level can remain very nearly constant over wide range of input and demand. In addition, the use of two hormones makes the system stable against relatively large perturbations in either direction.

An important feature of the model is that the set point is not fixed by an external reference but arises out of the dynamics, in particular out of the relation between the rates of production of the two hormones. The model therefore predicts that the consequence of an inability to produce insulin will be not just that the control will be less effective but that the set point will be shifted. This allows us to explain why patients with untreated Type I diabetes mellitus have high blood glucose levels even under conditions of low glucose input, and why it is difficult to maintain the normal level of 5 mmol/l in patients who are being treated with insulin. It also explains why Type II diabetes is easier to treat.

Introduction

One of the most important properties of the body is homeostasis, its ability to maintain a stable internal environment as conditions change. In particular, there are a number of regulators which closely control particular variables such as blood glucose, plasma sodium, plasma calcium, blood volume, etc. These have some significant features in common. First, they involve pairs of hormones, glucagon and insulin for blood glucose, calcitonin and parathormone for calcium, etc. Second, each of the pair of endocrine tissues inhibits secretion by the other. Finally, they are remarkably effective regulators. For example, during exercise the rate of glucose utilisation can rise by a factor of 10, with little or no change in blood glucose concentration. How the body controls the level of blood sugar is, in general terms, well understood. How it controls it so closely is not.

It is, to be sure, very difficult to elucidate the details of the mechanisms by which such control is achieved. Any physiological regulatory system is embedded in a complex of other systems. In addition to feedback control, there are typically feed-forward mechanisms which buffer against sudden shocks. When we have a meal, the blood insulin level rises before any additional glucose has entered the blood. Moreover, there can be alternative methods of controlling a variable, at least in the short term. If the body loses its capacity to produce, for instance, glucagon, glucose can be regulated by adrenalin and other hormones, albeit not as effectively and not for a long period of time. These properties are obviously beneficial, but they make it difficult to experiment or to interpret the results of observations on patients.

In this paper we show that the three features that we mentioned above are connected. If control is by two hormones which act in opposite directions and if each of the pair inhibits the secretion of the other, then zero steady state error can be achieved. Our model is quite general and utilises a principle which we call *integral rein control*, essentially two linked integral controllers. We illustrate it with an example which is consistent with what is known about the control of blood glucose by insulin and glucagon, though even this well studied system is not understood in sufficient detail to allow us to model the processes in detail. In particular, our model provides an explanation of why Type I diabetes, (*i.e.* the inability to produce insulin) cannot be managed by controlling the diet, and why it is difficult to maintain accurate control of the blood glucose levels even when insulin is being supplied, whereas Type II diabetes (in which insulin can be produced but is utilised inefficiently or not at all) can often be managed without supplying insulin. From our model, we suggest hypotheses about the islets of Langerhans which can be investigated.

Throughout this paper, we shall use the control of blood glucose by insulin and glucagon as the chief example, but most of the discussion applies *mutatis mutandis* to other systems as well. We provide here sufficient detail to allow a non-physiologist to follow the discussion; for more see Koeslag *et al* (1997).

The principle on which our model operates is drawn from the hypothetical Daisyworld of Watson and Lovelock (1983) (see also Saunders, 1994) in which black and white daisies combine to maintain a nearly constant planetary temperature

despite a large variation in the luminosity of the nearby star. Our model is actually slightly simpler mathematically, because Watson and Lovelock introduced microclimates and heat flow on the surface of the planet to make their model more realistic as a model of the Earth. The original model produces a negative steady state error, *i.e.* a finite error in the direction *opposite* to that of the input — as the solar luminosity increases the planet actually becomes cooler. Our model produces zero steady state error if the interaction between the hormones is symmetric; if it is only approximately symmetric then there is a small but finite error which can be in either direction depending on the details of the interaction. This demonstrates first that the mechanism is structurally stable and second that zero steady state error is not so difficult to achieve as one might imagine, since it is not at the very extreme end of what is possible by integral rein control.

The Problem:

The body is able to maintain the blood glucose level very nearly constant at 5 mmol/l. It can do this even though on the one hand, the amount of glucose entering the system may increase greatly after a meal, and, on the other, during exercise the amount that has to be supplied to the muscles may rise by a factor of 10 or more. It is especially remarkable that in the latter case the body achieves such a large increase in flux with little or no change in blood concentration. The value also does not change significantly with age, and it is the same in many other species, including of course the laboratory rats on which many of the experiments on insulin production have been performed.

Where a system must be able to maintain a constant level despite major perturbations of long duration, or even permanent changes in some parameters, an engineer would be likely to employ ‘integral control’. This involves feeding back a signal proportional to the time integral of the error. The controller operates until the error (the difference between the actual and desired outputs) vanishes and so ‘zero steady state error’ is achieved.

This is not what the body actually does, at least not exactly. If it were, the control would only involve one hormone, not two. As Clynes (1969) pointed out, using two hormones has the advantage that it makes the control equally effective against perturbations in either direction. If the blood glucose is too high, insulin is produced. If the blood glucose is too low, then this is corrected not simply by reducing the production of insulin and passively waiting for it to be removed from the blood. Instead, glucagon is produced, and this actively promotes a rise in glucose. Clynes gave this principle the name “rein control”.

We might therefore expect that a typical hormonal control system should combine rein control, to be effective in both directions, with integral control, to achieve zero steady state error. Unfortunately, the two are not compatible. An integral controller will operate until the error is zero. If there are two independent integral controllers in a system, then unless the set points are precisely the same, which cannot be guaranteed in any real system, least of all in physiology, at least one of them (in practice, generally both) will always be operating. Hence a proper steady

state cannot be achieved, even asymptotically.

Yet this does appear to be what the body does. We know that these systems typically involve two hormones. Moreover, it does appear that integral control or something very much like it is being used. We infer this partly from the fact that the body is capable of achieving zero steady state error, but also because it is what we would expect in such systems. Because the activities of the controllers, *i.e.* the concentrations of the hormones, are themselves governed by first order differential equations, they will appear in the equation for the controlled variable as integrals.

One way around this apparent impasse is to provide a link between the two controllers. In particular, if each inhibits the other, then not only can the system reach a stable steady state, but the equilibrium point can be fixed in a very simple and robust manner. This is clearly desirable in a system which is natural rather than engineered. And, as we have already mentioned, in these hormone pairs it is indeed typical that each inhibits the production of other.

The Model:

We are concerned here with the control of glucose by glucagon and insulin. We are dealing with the situation after any feed-forward control has had its effect and in which control by adrenalin or other hormones has not been stimulated. We acknowledge that this makes the model incomplete and limits the ways in which it can be tested, but our primary aim is to show how the actions of these two hormones alone could combine to produce zero steady state error.

We denote the glucose, glucagon and insulin concentrations by G, A, B respectively. We suppose that the blood glucose concentration is governed by an equation of the form

$$dG/dt = I + \alpha(A, G) - \beta(B, G) - \gamma(R, G) \quad (1)$$

Here I is the input of glucose into the blood, $\alpha(A, G)$ and $\beta(B, G)$ represent the effects of glucagon and insulin, respectively, on the blood glucose concentration, and $\gamma(R, G)$ represents the uptake of glucose by muscles and other tissues. The uptake is of course largely determined by the activity of the organism, and this is represented by the externally determined quantity R . We suppose that $\alpha(A, G)$, $\beta(B, G)$ and $\gamma(R, G)$ are all non-decreasing functions of both their respective arguments and that $\gamma(R, 0) = 0$.

We also suppose the hormone concentrations satisfy the equations

$$\frac{dA}{dt} = A(\phi(G)h_1(A, B) - D_{(A)}) \quad (2)$$

$$\frac{dB}{dt} = B(\psi(G)h_2(A, B) - D_{(B)}) \quad (3)$$

where $\phi(G)$ is a decreasing function of G and $\psi(G)$ is an increasing function of G . The functions $h_i(A, B)$ represent the mutual and self inhibitions, and should therefore satisfy

$$\partial h_i / \partial A < 0 \quad \partial h_i / \partial B < 0 \quad (4)$$

In the general case, we can set the derivatives equal to zero in (1),(2) and (3) and solve to obtain the steady state values $\tilde{G}, \tilde{A}, \tilde{B}$. If, however, the two inhibition functions $h_1(A, B)$ and $h_2(A, B)$ are equal, in which case we can write them as simply $h(A, B)$, then (2) and (3) imply

$$\phi(\tilde{G}) = (D_{(A)}/D_{(B)})\psi(\tilde{G}) \quad (5)$$

We can solve this equation for \tilde{G} immediately. We then use either (2) or (3) to determine $h(\tilde{A}, \tilde{B})$ and then, using (1), we can find \tilde{A} and \tilde{B} separately.

The system then has the following distinctive properties. First, it exhibits zero steady state error. No matter what the input to the system or the demand for glucose are, so long as there is an equilibrium state with both hormones present, \tilde{G} , the steady state value of the glucose concentration, remains the same. What changes are the hormone concentrations.

Second, the value of \tilde{G} is independent of the functions that appear in equation (1). It is determined by the functions $\phi(G)$ and $\psi(G)$ and by the ratio $D_{(A)}/D_{(B)}$. This means that the value of \tilde{G} depends on things that are comparatively easy to specify: the production rates of the hormones as functions of G and the ratio of the rates at which they are removed from the blood (and not the rates themselves, which would be less reliable). It also is not affected by the rates at which insulin and glucagon act to decrease or increase the glucose concentration, which might well depend on other factors as well. If, for simplicity but without affecting the argument, we set $D_{(A)} = D_{(B)}$, then \tilde{G} is that value of G at which the plots of $\phi(G)$ and $\psi(G)$ intersect.

The model therefore suggests a principle by which a variable can be maintained at a constant level and with the additional property that this desired level is itself easy to set reliably.

The form of equation (1) is largely irrelevant to the control, which is why it can be written in such a general form. On the other hand, while equations (2) and (3) also involve unspecified functions, they are of a particular form and have the additional requirement that the two inhibition functions should be the same. (To be precise, while this is sufficient for zero steady state error, it is not necessary. What is required is only that the equations $dA/dt = 0$ and $dB/dt = 0$ have a unique solution for G . Equations (2) and (3) seem to us to be the most plausible class with this property, but they are obviously not the only ones.) This provides an opportunity for an empirical test. If there is not a more or less symmetric mutual inhibition between the two hormones, this would be evidence against the model. Note that precise symmetry is not required for the principle to operate; the model is structurally stable and if the forms of $h_1(A, B)$ and $h_2(A, B)$ are close but not exactly the same, then there will be a finite steady state error but it will be small.

In the case of blood glucose regulation, we can see why equations (2) and (3) or something close to them might apply. Glucagon and insulin are secreted by α - and

β -cells, respectively, which are located in the islets of Langerhans in the pancreas. (There are also somatostatin-secreting D-cells, but we are not including these in the model.) At rest a healthy pancreas secretes both insulin and glucagon; after a meal or during exercise both are still secreted but in different proportions. An increase in glucose concentration will induce an increase in insulin concentration, and it is believed that this is brought about by an increase in the number of β -cells entering into a state with Ca^{+2} -induced secretory pulses, rather than by a graduated response involving all the β -cells simultaneously (Schuit *et al*, 1988; Pipeleers, 1992; Hellman *et al* 1994; Pipeleers *et al* 1994).

We have proposed (Koeslag *et al*, 1997) that small groups of α - and β -cells, linked by gap junctions, function as syncytia. As β -cells switch on or off, α -cells make the opposite switch. In addition, an insulin-secreting syncytial group would promote its neighbours, possibly via a paracrine secretion, also to switch to insulin secretion. Similarly, a glucagon-secreting group would promote its neighbours to switch to glucagon secretion. At blood glucose levels above 5 mmol/l, insulin groups would be more effective at promoting switches; below that level glucagon groups would be more effective.

Why Two Hormones?

As we mentioned above, Clynes (1969) suggested that the advantage of rein control is that it is equally effective in both directions. This is so, although we doubt that it is important for small perturbations in blood glucose because both insulin and glucagon disappear quite rapidly from the blood. This system is, however, subject to large perturbations in either direction. If, for example, only insulin were used, then the body could cope with a large increase in demand only by a large decrease in the insulin level. The level under normal conditions would therefore have to be very high. In contrast, in a two-hormone system, under normal conditions of input and demand, it is not hard to arrange that the glucose level would be at its proper level if there were neither insulin nor glucagon present. This not only seems a natural state of affairs, it also means that if approximately normal conditions are maintained for some time, the system can gradually reduce the amount of both hormones, so long as the balance between the two is correct.

Even more than that, however, single-hormone integral control is difficult to arrange. Imagine a system without glucagon, and suppose that the equations governing the concentrations of glucose and insulin are

$$\dot{G} = \dot{G}(I, R, G, B) \quad \dot{B} = \dot{B}(B, G) \quad (6)$$

where a dot denotes differentiation with respect to time. We can readily determine the steady state values of G and B by solving the equations $\dot{G} = 0 = \dot{B}$. In general, these will depend on I and R . For \dot{G} to be independent of I and R , the expression for \dot{B} must factor:

$$\dot{B} = f_1(B)f_2(G) \quad (7)$$

Such an expression would be plausible if we were concerned only with the production of insulin, but we also have to include in the model its removal from the system. It seems unlikely that this should be dependent on the glucose concentration, still less that it should be dependent on it in the same way as the production. If, in particular, we make the natural assumption that the rate of removal of insulin should be proportional to its concentration, equation (7) would have to be of the form

$$\dot{B} = B(\psi(G) - D) \quad (8)$$

i.e. the rate of production would also have to be exactly proportional to the concentration. What is more, since at equilibrium $\psi(\tilde{G}) = D$, the specific rate of removal would have to be set precisely to achieve the desired value of \tilde{G} . In the case of two hormones, what matters are not the rates of removal but only the ratio of the two, which is much more easily specified and more likely to remain approximately constant as conditions change.

Integral rein control depends on the production of the two hormones being inhibited in the same way. As we have suggested above, this could happen if they are produced by cells that are physically close together and compete in some way, though this is not the only possibility. In contrast, integral control by a single hormone requires one particular production function and a rate of removal which is constant and at exactly the required value.

There is, however, a drawback to integral rein control. In both proportional control and integral control, it is usual that under “ideal” conditions, *i.e.* when the external parameters have their nominal values, the system will be at the set point and the controller (or controllers, in the case of rein control) will not be operating. This means that if a controller fails, partially or altogether, then providing the conditions remain ideal, the system will remain at the set point. It may therefore be possible to control it by other means, at least against small perturbations. In principle, one could compensate for small changes in the glucose level by carefully adjusting the input.

The situation is quite different with integral rein control, because under ideal conditions both controllers are active. If one of them fails, therefore, the other will drive the system away from the set point. The system may still reach an equilibrium, but it will not be at the required value. In the particular model we shall discuss later, and also in patients with Type I diabetes mellitus, the new equilibrium is well above the level of the normal one. Any alternative controller must be able to counter this, not merely compensate for small perturbations. Thus the principle of integral rein control can explain why patients with Type I diabetes mellitus must be treated with insulin if they are not to exhibit raised blood glucose levels even under conditions of very low input of glucose. The inability of the body to produce insulin does not simply reduce its capacity to maintain the desired set point of 5 mmol/l; it actually moves the set point. More precisely, instead of a set point there is now an equilibrium glucose level which varies with both input and demand. To achieve a level of approximately 5 mmol/l now requires a form of intervention that

is capable of holding the system away from this equilibrium. Moreover, because 5 mmol/l is no longer an equilibrium value for the system, it is difficult to maintain this level with any accuracy unless the intervention can be very precisely controlled.

Note that the location of the set point is associated with the mechanisms of production of insulin and glucagon, not with their utilisation. If, for example, insulin can be produced normally but is less effective in removing glucose from the blood, the model predicts that the set point will remain at 5 mmol/l, though the range of input over which this level can be maintained will be reduced. Thus the model predicts that the symptoms of Type I and Type II diabetes should be different, and that in particular, while patients with Type I diabetes will always require treatment with insulin, those with NIDDM (noninsulin dependent diabetes mellitus) may be able to maintain a normal blood glucose level by other means, as is indeed the case.

Finally, if both controllers fail, then the model reduces to

$$\frac{dG}{dt} = I - \gamma(R, G) \quad (9)$$

The equilibrium value \tilde{G} , where it exists, is dependent on the input and the demand, and is stable, because we have supposed $\partial\gamma/\partial G > 0$. Note that in this case it is generally possible to choose I and R to make \tilde{G} equal to 5 mmol/l (or any other reasonable desired value), which means that (in principle, at least) the blood glucose level could be controlled by sufficiently close regulation of input and demand. A partial failure of an integral rein control system can make the normal set point unattainable; a total failure may only make it very difficult to maintain.

An Example:

To illustrate how a system of the kind we propose would behave, we now replace the unspecified functions of the previous sections by particular examples. The choice is not critical, and the parameters have been chosen more or less arbitrarily. The aim here is not to justify in detail a proposed mechanism but to show that zero steady state error over a wide range of inputs and demands is easily achieved using simple functions and to discover some of the properties such a system would exhibit.

For the response of α - and β -cells we use:

$$\begin{aligned} \phi(G) &= \begin{cases} 1, & G < 2.5 \\ 1 - (G - 2.5)^2/25, & 2.5 < G < 7.5 \\ 0, & G > 7.5 \end{cases} \\ \psi(G) &= \begin{cases} 0, & G < 2.5 \\ 1 - (G - 7.5)^2/25, & 2.5 < G < 7.5 \\ 1, & G > 7.5 \end{cases} \end{aligned} \quad (19)$$

This choice locates the constant steady state at $\tilde{G} = 5$ and $\phi(\tilde{G}) = \psi(\tilde{G}) = 0.75$. We also set $D_{(A)} = D_{(B)} = D$ which simplifies the calculations but makes little real difference.

We take

$$h(A, B) = K - A - B \quad (20)$$

We make this choice partly on grounds of simplicity and partly because it is consistent with our flip-flop hypothesis. The parameter K might depend on the somatostatin concentration, but here we take it to be constant. We take $\alpha(A, G) = \alpha A$, $\beta(B, G) = \beta B$, $\gamma(R, G) = RG$, where α and β are constants, so that equation (1) becomes

$$dG/dt = I + \alpha A - \beta B - RG \quad (21)$$

The eigenvalue equation is then

$$0 = \begin{vmatrix} -3A/4 - \lambda & -3A/4 & -4AD/15 \\ -3B/4 & -3B/4 - \lambda & 4BD/15 \\ \alpha & -\beta & -R - \lambda \end{vmatrix} \quad (22)$$

The sum of the eigenvalues is $-0.75(A + B) - R$, and as long as $G = \text{const.}$, this varies linearly with R and is independent of I . Under ‘ideal’ conditions, $A = B$, and (22) reduces to

$$0 = (\lambda + 3A/2)(\lambda^2 + R\lambda + 4AD(\alpha + \beta)/15) \quad (23)$$

and the eigenvalues are therefore

$$\lambda_1 = -3A/2 \quad \lambda_{2,3} = \frac{1}{2} \left[-R \pm \sqrt{R^2 - 16AD(\alpha + \beta)/15} \right] \quad (24)$$

Thus the equilibrium is stable providing only that the parameters are positive.

For the numerical calculations we set $K = 6$, $D = 0.1$, $\alpha = \beta = 2.9$, and we took the nominal values of I and R to be 1 and 0.2, respectively. In Fig. 1, we show the effect of gradually increasing the demand R from 0.2 to 5.0 and then reducing it gradually 0.2. In Fig. 2, we show the effect of gradually changing the input I from 1 to 19 and back. In both cases the glucose concentration remained almost constant for a long time despite the large increase in demand or input. Only when the change had reached the point that one of the hormones disappeared altogether from the system did the glucose concentration show a significant response.

[Figs 1 and 2 about here]

In both cases the system mostly passed through a succession of equilibrium values and the concentrations were therefore as found in the stability analysis. The chief exception was that as the control variable (I or R) was being reduced after having been raised to a very high value, the system remained for a short time in the steady state with A or B (respectively) equal to zero, even though this was now unstable. This happened even though a small perturbation in these variables had been incorporated into the program specifically to avoid it. We could have eliminated this feature by using some other form of perturbation, but we have left

it in to remind us that if our cell recruitment model is correct, the body might well take longer than expected to recover from an excessive increase in input or demand because there would be so few β or α cells, respectively, from which to start. In general, we expect over- or undershoots to occur when part of a system has been effectively shut down and has to be reactivated.

Because equations (19) and (20) are meant as illustrations and not as detailed models of the system, the actual values of most of the parameters are of little significance. On the other hand, in any control problem the ratio between the characteristic time scales of the controllers and the likely perturbations can be very important. In this model, the controller time scale is specified by the parameter D ; if no hormone is being produced then the concentration in the blood decreases according to the relation $A = A_0 e^{-Dt}$.

In the calculations for Fig.2, the glucose input was assumed to increase linearly: $I = 1 + 0.01t$. If we suppose that I doubles in half an hour, which is typically what happens when a healthy person takes 50g of glucose all at once, then setting $D = 0.1$ makes the half life of the hormones in the blood about 2 minutes, so the ratio between the time scales is of the right order. Even if we speed up the rate of increase of glucose by a factor of 10 (or, equivalently, suppose that the characteristic time for the hormones is longer by the same factor), the results are not greatly affected: as I rises from 1 to 10, G peaks below 5.7 and soon stabilises between 5.5 and 5.6. Of course this is the transient response; if I remains constant at 10, G soon falls to its equilibrium value of 5.0.

We can simulate Type I diabetes mellitus by setting $B \equiv 0$. In that case, using the nominal values $I = 1$, $R = 0.2$, we find $G = 7.5$, well above the optimal value, and $A = 0.17$, less than normal but still nowhere near zero. If we increase I , G remains approximately constant (albeit at too high a level) and A decreases until at about $I = 1.6$ it has almost disappeared. If I is increased further, G increases proportionately.

If, on the other hand, we increase R , then G remains approximately constant for much longer; when $R = 2.0$, ten times the nominal value, G has only fallen from 7.5 to just 7.3. In the absence of insulin, the glucagon is serving as a one-sided integral control system, doing its best to hold the glucose level at the (incorrect) set point and thus making the desired level of 5.0 very difficult to attain. As R is further increased, G then falls, but it does not reach the value 5.0 until $R = 3.6$, which is the extreme end of the range of constant G under normal conditions, *i.e.* when both glucagon and insulin can be produced. (See Fig. 3)

[Fig. 3 about here]

A key point of the two hormone model is that the equilibrium value \tilde{G} depends not on the values of the hormone concentrations A and B but on the balance between the two. For values of R and I not too far from normal, reducing K reduces the values of A and B but does not change the value of \tilde{G} . It reduces the range within which \tilde{G} can be maintained at the desired value and it may reduce the rate at which the system returns to equilibrium. In the model, K represents the total number of α or β cells which can be switched on. If K could somehow be reduced under

normal conditions but increased under stress, the system would achieve just as good regulation but with a lower total production of hormones except when responding to a large perturbation.

We would expect something similar in all forms of integral rein control. Mathematically, we are not working directly with two physical variables, here A and B , but with two functions of them, $u(A, B)$ and $v(A, B)$, say. These represent a combination of the two physical variables and the balance between them. In the simplest case, u could be the sum $A + B$ (as here) and v the ratio A/B , though in general they might be far more complicated.

In terms of the new variables it is essentially v that is responsible for the control. In the glucose example, a change in input or demand is met by a change in the balance between glucagon and insulin. The value of u is held fixed, and its only role is to determine the range over which integral rein control can operate. Thus the present simple model is chiefly concerned with only one of the control variables, v . There is, however, a second variable, and we would expect that in a real system it too would play a role. The most likely, as we have suggested, is to reduce the amount of effort required for regulation under small perturbations from normal. If this is so, then we would expect to find that coping with a long term but moderate perturbation should require increased activity of the controllers and presumably produce signs of stress in the system, even though the variable in question remained as well controlled as under normal conditions.

The same transformation from two physical variables to two representing essentially their sum and balance is common in applications of catastrophe theory (e.g. Zeeman, 1977, Saunders, 1980). In such cases, so long as u is small, the system typically responds smoothly to changes in v , but sudden jumps can occur if u is large. This can lead to counterintuitive behaviour of the sort described by Seif (1979) in his analysis of hypo- and hyperthyroidism. Seif's model explains why while a transition from hypothyroidism to euthyroidism is comparatively straightforward, a smooth transition from hyperthyroidism to euthyroidism can be achieved only via hypothyroidism, not directly. The effect of the second control variable may not be as dramatic in other examples, but it should still be investigated.

[Figs 4 and 5 about here]

We have computed the eigenvalues of the stability matrix (equation (22)) for different combinations of I and R . The real parts are plotted in Figs 4 and 5. Note that as R increases, there is at first only one real eigenvalue, then three and then, just as the equilibrium becomes unstable, only one again. The result is that even though the sum of the eigenvalues increases linearly with R (as can be seen from (22), bearing in mind that $A + B = \text{const.}$) the resilience, measured by the magnitude of the least negative real part, first rises and then falls. If I is increased, the resilience remains very nearly constant, with again a change from a focus to a node shortly before the equilibrium becomes unstable.

We also tried the effect of letting I and R vary together while maintaining the relation $I = 5R$. This was to represent a system in which a somewhat larger or smaller input had persisted for a long time and the demand had been adjusted to

compensate. In this case, the resilience varied linearly with R but more markedly than before, because A and B also changed.

We have repeated the calculations taking $\alpha(A, G) = \alpha AG$ and $\beta(B, G) = \beta BG$. This made relatively little difference to the results, except that when the system was beyond the range in which zero steady state error could be maintained, the effect of changing the input I was less but that of changing the demand R was greater.

Mathematically, the zero steady state error is a consequence of the relation $h_1(A, B) \equiv h_2(A, B)$. We have justified this assumption by our earlier proposal (Koeslag *et al*, 1997) that groups of α - and β -cells function as syncytia, but even if we are right, we cannot assume that the two functions will be precisely the same. To investigate what difference this makes, we have carried out calculations using

$$\begin{aligned} h_1(A, B) &= K - (1 + \gamma)A - (1 - \gamma)B \\ h_2(A, B) &= K - (1 - \gamma)A - (1 + \gamma)B \end{aligned}$$

The most important finding is that the system is structurally stable, as indeed the relatively simple forms of equations (1)-(3) would suggest. For small values of γ , the steady state error is small. If $\gamma > 0$, *i.e.* if each hormone inhibits itself more than it inhibits the other, then the equilibrium value \tilde{G} decreases with the demand R and increases with the input I , as we would expect. For example, if $\gamma = 0.05$, then doubling R from its nominal value of 0.2 decreases \tilde{G} from 5.0 to 4.6, and doubling I from its nominal value of 1.0 increases \tilde{G} from 5 to 5.4. Note that even though γ is small, the ratio h_1/h_2 is approximately 0.8, so this represents a considerable deviation from symmetry.

If, on the other hand, $\gamma < 0$, then \tilde{G} increases with R and decreases with I . Thus this system can, like the Daisyworld model, exhibit negative gain, *i.e.* a finite error in the direction opposite to the perturbation. This is a distinguishing feature of systems in which the fixed point is determined dynamically; proportional control cannot produce negative gain.

Conclusions

Integral rein control provides a means by which zero steady state error can be achieved even under relatively large perturbations in either direction. It explains how such precise control can be achieved, why it involves pairs of hormones and why these not only have opposite effects but also inhibit each other. The set point is determined by the intersection of two chemical response curves, which makes it robust and in particular can explain why it typically remains constant throughout the life of an individual and is the same for individuals of the same or even related species. The model also predicts that if one of the controllers fails or is seriously damaged, the system will in general still have a stable steady state but even when the external parameters have their nominal values this will not be the normal set point. This explains why a patient with untreated Type I diabetes mellitus will have a high blood glucose level even when the input of glucose is low, and why it is not in general possible to treat the condition merely by restricting the input of

glucose, nor to maintain a level of 5 mmol/l except by very close control of the supply of insulin.

In contrast, so long as the controllers are operating properly, the set point will be maintained even if the system is not responding properly to the control. This may account for many of the differences between the two kinds of diabetes, and in particular may explain why Type II diabetes may be manageable without supplying insulin.

Not enough is known about the details of the mechanism of glucose regulation to allow us to complete the model, but in its present form it is consistent with what we do know. The conditions for integral rein control are sufficiently unrestrictive that we expect to observe it in other systems as well, although the nature of the link between the two controllers could vary from case to case. It is also relatively easy to see how an integral rein control system can arise in evolution, since it is the combination of two simple systems each of which could have appeared separately and would have been useful by itself. The distinctive feature, the zero steady state error, arises when they interact. It is not a product of direct selection. Moreover, we would expect integral control (rein or otherwise) to have appeared in such systems because it arises more naturally than proportional control (through simple chemical rate equations) rather than because it has the advantage of achieving zero steady state error — though of course once it appeared it would tend to be preserved for that reason.

While the model is successful in that it achieves zero steady error and links it to other observed properties of a class of regulators, it is not easy to test it further by direct experiment, because of technical difficulties and interference from other regulatory systems. We already know what happens for small and medium perturbations, and it is not easy to design an experiment which will test what one system alone will do under large ones.

The model does, however, lead to testable predictions. For example, we have suggested (Koeslag *et al*, 1997) that the α and β cells in the islets of Langerhans act as syncytial groups, and this is open to empirical test. Integral rein control requires a close interaction between the two controlling elements, and this should be sought in any example in which it is supposed integral rein control may be involved. Where it is found, this would be evidence in favour of the hypothesis; where it cannot be found, this would be evidence against it.

More generally, our analysis shows that where a partial failure of a control system has the consequences that (a) the system does not maintain the desired level even when the input and output have their nominal values and (b) it is difficult to achieve and maintain the desired level with any precision by intervention, this is strong evidence that the set point is determined dynamically and not by comparison with an external reference. In particular, we would predict that this is so in the case of the control of blood glucose.

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Figure Captions:

Fig. 1 Dependence of blood glucose G on demand R as R is gradually changed to 25 times its nominal value and then back.

Figure 2. Dependence of blood glucose G on input I as I is gradually changed to 20 times its nominal value and then back.

Figure 3. Simulation of diabetes mellitus. This figure shows the dependence of blood glucose G on demand R as R is gradually changed to 25 times its nominal value and then back, assuming that insulin cannot be produced.

Figure 4. Real parts of the eigenvalues of the stability matrix for the system given by equations (19) and (20), for different values of the demand R .

Figure 5. Real parts of the eigenvalues of the stability matrix for the system given by equations (19) and (20), for different values of the input I .