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# Silent Endocrine Tumors

## A Steady-State Analysis of the Effects of Changes in Cell Number for Biological Feedback Systems

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**Abstract**. Some tumors of hormonal organs are clinically active, while others are not. The "silent" tumors may be discovered by accident or because of effects due to their increase in size. From a simple steady state analysis of hormonal feedback systems follows that hormonal cell multiplication does not significantly influence the systems steady state behavior (hence the clinical silence). — Exceptions to this rule occur in three situations: when the gain of the system is low; when the growth concerns cells with isolated sensor or reference functions; or because of the growth of autonomous cells. In many biological systems the dangerous situation of clamping to low levels upon sensor cell multiplication has been prevented by lumping, such as the combination of sensor and comparator functions into sensor-comparator cells.

### Introduction

Diseases in which the level of hormonal activity is increased are no rarity. In several instances such a disease is caused by a proliferation of active hormonal cells. The number of cells is increased: slightly (a hyperplasia) or more numerous and benign (adenomas) or malign (carcinomas).

Endocrine adenomas without a concomitant increase of the corresponding hormonal level are also no rarity, however (cf. Labhart, 1974). In these cases no overt hormonal disease exists clinically. Many are discovered by accident upon autopsy. In other instances they are detected because of the effects caused by their increase in size: a swelling or lump as such; or because of their effects upon the surrounding tissue, which may atrophy and then gives rise to clinical symptoms. Many examples for different endocrine systems can be found in the standard textbooks on endocrinology (e. g., Labhart, 1974; Williams, 1974); sometimes accompanied with the remark that this phenomenon is not understood, especially since their histological appearance, suppression tests or radio-immunological assays suggests or show that the cells of these tumors are hormonally active. In such cases the sometimes quite large increase in the number of active cells does not cause hormonal overproduction. This goes against intuition. Since the corresponding hormonal state of these patients lies within normal limits, the clinical inactivity of these tumors may, therefore, be confused with hormonal inactivity. Names such as "endocrine-inactive chromophobe adenomas" (of the pituitary), "hormonal-inactive parathyroid adenomas", "inactive beta-islet cell adenomas" or "inactive adrenocortical adenomas" exemplify this situation.

In the following it will be shown, with the use of a simple analysis, that upon multiplication of hormonal cells:

a) clinical normalcy is expected to be the rule rather than the exception (unless the system is weak, i.e. has a low gain),

b) when a deviation occurs, a clinical state of *sub-normal* activity must be expected in some instances of cell growth,

c) that this class of diseases is ruled out for many hormonal systems by a combination of functions into single cells,

d) that hormonal overproduction often is indicative of a further "development" of the tumor: autonomous activity, i. e. input-independent activity.

### Steady State Feedback Diagram

Many endocrine organs are involved in homeostatic control of the level of a hormone or of a substance such as glucose or calcium ion. In the following the effects of changes in cell number are, therefore, calculated for a

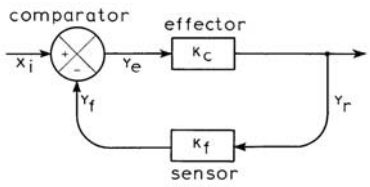


**Fig.1.** Steady state feedback diagram. Regulated state $y_r$; feedback signal $y_f$; reference $x_i$; error signal $y_e$; effector gain $K_c$ and sensor gain $K_f$

feedback control system of which the elements are endocrine cells. Since the processes under consideration are relatively slow, a stationary state analysis suffices, where the properties of the system elements may be represented by multiplication factors (gains: $K$ ). First consider the feedback diagram of Fig. 1. The level of the regulated variable $y_r$ (index $r$ from *regulated*) is measured by a sensor. This element is often not explicitly indicated in hormonal feedback diagrams inspired by the anatomical structure of the system. The sensor sends the feedback signal $y_f$ (index $f$ from *feedback*) to the comparator. This transduction (it signals the level of $y_r$ by the generation of another substance $y_f$ ) involves multiplication with a constant $K_f$ , the feedback gain of the system, i. e.

$$y_f = K_f\, y_r. \tag{1}$$

The comparator compares the feedback signal $y_f$ with a reference signal $x_i$ generated elsewhere (another hormone) or within the comparator element itself. The reference signal is indicated here by $x$, since it is an independent variable (the $y$'s are dependent variables) and the index $i$ indicates that it represents the *ideal* state. Since comparison can be done by subtraction, the comparator output is written

$$y_e = x_i - y_f\,. \tag{2}$$

Here $y_e$ is the error signal (index $e$ from *error*) which is sent to the corrector (or effector) element. The effector generates the regulated state $y_r$ . Hence:

$$y_r = K_c\, y_e\ . \tag{3}$$

Its action is proportional to the error signal, indicated by the effector gain $K_c$ (index $c$ from *correction:* it corrects changes of the regulated state). Substitution of (1) into (2) and the result into (3) gives the regulated state $y_r$*:*

$$y_r = \frac{K_c}{1 + K_f K_c}\, x_i\,. \tag{4}$$

The coefficient of $x_i$: $K_c/(1+K_f K_c)$ is called the *closed loop gain* of the system.

Assume that the system is at the ideal state $y_i$ at some point in time. The effector does not need to correct, hence the error signal $y_e$ is zero, and the feedback signal $y_f$ is equal to the reference $x_i$ (2). From (1) follows for the ideal state $y_i$:

$$y_i = \frac{x_i}{K_f}\,. \tag{5}$$

Insertion of (5) into (4) gives

$$y_r = \frac{\mathrm{K}}{1 + \mathrm{K}} y_i \tag{6}$$

where the (*open loop*) *gain K* is given by

$$K = K_f K_c\ . \tag{7}$$

The coefficient of $y_i$ in (6) is the *feedback ratio* of the system: the quotient $y_r/y_i$. It indicates how closely the actual state $y_r$ lies to the ideal state $y_i$. It follows that the system described belongs to the class of proportional control systems.

## Ideal State and Reference

The relationship between the ideal state $y_i$ and the reference $x_i$ expressed by (5) is quite important for the understanding of biological feedback systems and their diseases. It is, therefore, to be deplored that the term "set-point" is quite often used indiscriminately for both the reference $x_i$ and the ideal state $y_i$. The confusion may have come about by a confounding with unity feedback systems in which the feedback is identical with the system output (the regulated state variable): $y_f = y_r$ in Fig. 1, $K_f = 1$ and $y_i = \mathrm{x_i}$. In calculations with block diagrams any feedback system can formally be written into the form of a unity feedback system, but in such cases the reference need to be transformed (5) (cf. DiStefano et al., 1967). It is hence advisable not to use the term "set-point". Three other arguments may also be brought forward in this respect.

1. The term "set-point" often is associated with the existence of a separate, anatomically and physiologically identifiable set-point *element.* A fallacy which has been pointed out, for instance, by Mitchell et al. (1970). A similar trap may, however, follow the use of the term "reference" when the idea of the existence of a reference *element* is stressed.

2. The term is suggestive of a rigidity of the feedback system, which leads to conceptual problems for systems in which the reference varies.

3. Equation (5) shows that control may not only be exerted via a change of the reference, but also via changes of the feedback gain $K_f$. Control via changes of the feedback gain probably is not often considered in the development of technical feedback systems; in

biological systems this kind of control may exist more often than we are inclined to think. The so-called gamma-control of muscle length via a change of the sensitivity of the sensors in muscle (the muscle spindles) forms an example. Mitchell et al. (1970) suggested that the control of fever by pyrogens is exerted by a change of feedback gain. The ideal state is, hence, a *dependent* variable; a notion which is lost when the term "set-point" is used for this state.

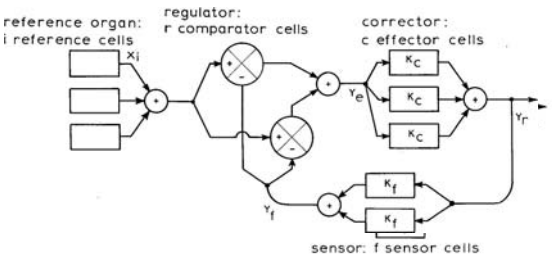


**Fig. 2.** Multicellular hormonal feedback system, in which each organ consists of a number of cellular elements. The organ output is mixed thoroughly (addition sign in circle) before it reaches the next organ

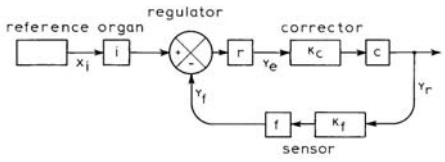


**Fig. 3.** Multicellular hormonal feedback system, with cell numbers written as additional serial gain elements

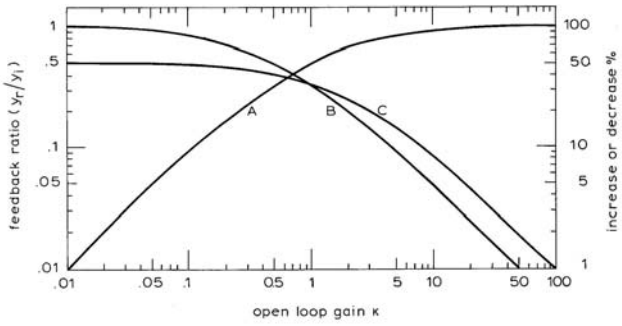


**Fig. 4.** Effects of changes in cell number. Curve A: ratio of the regulated state and the ideal state (the feedback ratio) plotted against open loop gain *K*. The percentage change of the feedback ratio upon a doubling of the gain (increase; Curve *B)* and after a halving of the gain (decrease; Curve C) plotted as functions of the original gain *K*

## Multicellular Elements

Consider a feedback system of which each element consists of many cells instead of one (as was assumed above). Each cell senses the state of the arriving hormone or substance, produced by the collection of cells of the former set of elements (Fig. 2). The combined sensor output (the feedback signal $y_f$ ) is now given by

$$y_f = f K_f \, y_r \,, \tag{8}$$

where $f$ is the number of sensor cells and $fK_f$ the feedback gain. The combination of comparator cells forms the regulator, for which

$$y_e = r(ix_i - y_f) \,. \tag{9}$$

Here $i$ indicates the number of reference cells, $ix_i$ the reference signal and $r$ the number of comparator cells of the *regulator.* For the corrector, with $c$ effector cells:

$$y_e = c K_c y_e \,. \tag{10}$$

Substitution of (8) into (9) into (10) gives

$$y_r = \frac{i\,r\,c\,K_c}{1 + f\,r\,c\,K_f K_c}\, x_i = \frac{f\,r\,c\,K_f K_c}{1 + f\,r\,c\,K_f K_c}\, y_i \tag{11}$$

where

$$y_i = \frac{i\,x_i}{f\,K_f}, \tag{12}$$

since at the ideal state $y_e = 0$ and $y_i = y_r$ in (8) and (9).

Equation (6) follows again after insertion of (12) into (11) with the (open loop) gain

$$K = f\,r\,c\,K_f K_c \,. \tag{13}$$

The system may, therefore, be drawn as shown in Fig. 3: the cell numbers function as additional gain components.

A multiplication of the effector cells and/or the comparator cells increases the *forward gain*[1] (Fig. 3):

$$K_G = r c K_c \,. \tag{14}$$

For sensor cells a multiplication increases the *feedback gain* $K_H$ (Fig. 3):

$$K_H = f K_f \,, \tag{15}$$

while an increase of the number of reference cells (if present) does not influence the gain. The reference input increases proportionally. A decrease of cell number gives rise to reverse situations.

## Cell Multiplication or Decrease

A change of the number of sensor, comparator or effector cells changes the gain $K$ of the system: it increases upon an increase of cell number and vice versa (13). For systems with a relatively large gain the feedback ratio $K / (1 + K)$ approaches 1 (Fig. 4). The

1 The symbols *G* and *H* are used here as indices of the lumped forward respectively feedback gains since they are in use to respectively indicate the forward and feedback *transfer functions*, while *K* is used for multiplication constants (cf. DiStefano, 1967)

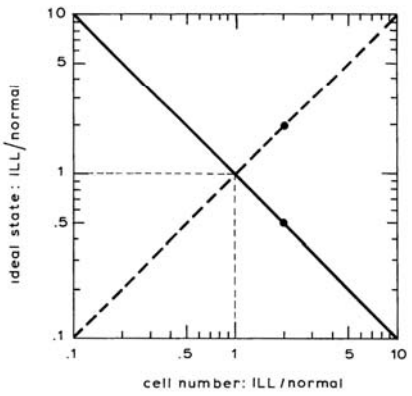


**Fig. 5.** Effects of changes in cell number. Normalized ideal state plotted against normalized cell number: for sensor cells (continuous line) and for reference cells (dashed line). Points: effect of a doubling of the number of cells

familiar property of feedback systems – their insensitivity to changes of the gain – follows from this relationship. Curve *A* (Fig. 4) shows the feedback ratio as a function of the (open loop) gain *K*. The percentage increase of the feedback ratio upon a doubling of the cells is given by Curve *B*, while the percentage decrease upon a loss of half the cells is depicted by Curve C. It follows that systems with gains between 5 and 10 are already quite effectively stabilized against drastic changes of the number of cells. Therefore, a change in cell number need not significantly influence the systems steady state behavior. This applies especially to changes of the number of the cells involved in the *forward gain* (14): effector or comparator cells. Only for weak systems the changes will quickly become clinically relevant; a situation which may apply to the prolactine hormone system, since small hypophysial tumors (microadenomas) significantly raise the level of prolactine. A similar situation may be the case for the growth hormone system.

Such a situation does *not* apply to changes of the *feedback gain (15).* A multiplication or decrease of the sensor cells quite drastically changes the ideal state $y_i$ of the system (12). Sensor cell multiplication drives the regulated state $y_r$ *down* [(12) and Fig. 5] and *clamps* it to the new state because of the increased loop gain *K* [(6) and Fig. 4]. Loss of sensor cells drives $y_r$ upward and decreases the gain of the system. Its regulated state is raised and labile. Possible candidates for this kind of disease may (again) be the growth hormone system and the prolactine hormone system.

Changes of the number (i) of reference cells also change the setting of the system (12) but now without a change of the gain *K* (13). In this case an increase of cell number raises the level of the regulated state $y_r$ and a decrease lowers it (Fig. 5).

*Conclusion.* For comparator cells and for effector cells increases of cell number do not influence the systems behavior significantly (when the original gain is large), while an *increase* of sensor cell number *decreases* the regulated state and *increases* the gain of the system. An increase of the number of reference cells raises the regulated state.

A decrease of the number of cells likewise does not influence the regulated state significantly (as long as the gain decrease is not too large). A decrease of the number of sensor cells raises the regulated state and weakens the system, while the regulated state goes down upon a decrease of the number of reference cells.

## Combination of Functions (Biological Lumping)

Relatively small changes of the backward gain or of the number of reference cells quite drastically change the regulated state because of their influence upon the ideal state $y_i$ (11) and (12). A change in the number of sensor cells has the additional effect of a change of the (open loop) gain *K*. Diseases causing the increase of the number of sensor or reference cells, or their decrease may, a priori, be considered to occur as frequently as similar diseases of the comparator or the effector. They are quite dangerous, however, which usually is not the case for the forward gain diseases. They also are rarely encountered in clinical practice in contrast to the expectation expressed before. How has this come about?

A) One answer to this question is for the vulnerable elements to consist of cells, which lost the ability to multiply after the juvenile stage (such as nerve cells). It must be kept in mind, however, that a) in such cases the number of sensor or reference cells may be too small or too large from the very beginning ("inborn" errors) and b) a decrease of cell number may still occur later in life.

B) A second answer follows from a consideration of the effects of the combination of functions within cells (biological lumping). When *all* elements are lumped into a single cell, then for an organ consisting of *c* cells the regulated state

$$y_r = \frac{c\,K_f K_c}{1 + c\,K_f K_c}\; y_i \text{ with } y_i = \frac{x_i}{K_f} \qquad (16)$$

and the effect of a change in cell number only influences the gain of the system, which in most cases is not harmful at all. One may speculate that such a situation may have been a starting point during evolution. A similar result follows when all elements are combined into one cell, but for the effector: i.e. for control systems with combined sensor-reference-comparator cells and separate effector cells.

An interesting situation is given by the combination of sensor and comparator functions (Fig. 6). Here

$$y_r = \frac{rcK_fK_c}{1+rcK_fK_c} y_i \quad \text{with} \quad y_i = \frac{ix_i}{K_f}. \tag{17}$$

In this situation the internal coupling of sensor and comparator functions has the result that the dangerous effect of clamping to a lower level *cannot* occur upon cell multiplication. It appears that many hormonal control systems exhibit the combination of functions within single cells; in all cases including the sensor function:

A) Sensor-comparator combinations exist, for instance, within the thyroxine control system and within the systems controlling the levels of cortisol and of the gonadal hormones, i.e. the basophilic cells of the anterior pituitary are sensor-comparator cells.

B) A lumping of sensor, reference and comparator functions occurs within the systems controlling the blood glucose levels (alpha and beta cells of the pancreatic islets) and those controlling the level of free calcium ions within the blood plasm (parathyroid cells, and the calcitonin cells within the thyroid). The mentioned cells can all be considered to be sensor-reference-comparator cells. The same situation may apply to the central heat-sensing cells (Mitchell et al., 1970).

Note that reference lumping does not imply a priori that external reference modifying inputs do not exist.

*Conclusion.* Lumping of the sensor element into sensor-(reference)-comparator cells completely avoids the danger of clamping the regulated state to a lower level upon cell-multiplication. One may infer that this effect has been of evolutionary significance (prevention of further de-lumping) in the development of many biological control systems. It follows that cell multiplication in general does not influence the systems steady state behaviour, unless the system is weak or in case the growth concerns cells with isolated sensor or reference functions.

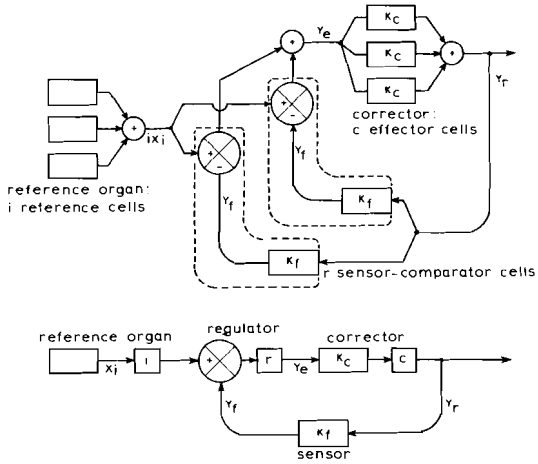


**Fig. 6.** Multicellular feedback system with lumped sensor-comparator cells (above) and its representation by additional serial gain elements (below)

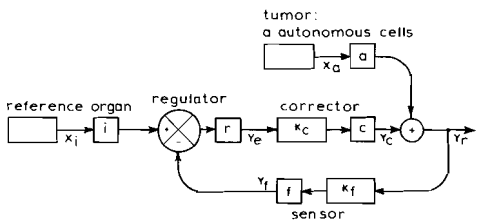


**Fig. 7.** Hormonal feedback system upon the development of an autonomous tumor of effector (-like) cells

## Autonomous Activity

The term autonomous activity indicates pathological production of output independent of cell input. In such cases the diseased cells do not form part of the regulating system anymore. Although such a growth may occur within the original organ, its anatomical location must not be confused with its functional situation with regard to the control system. Functionally autonomous elements lie outside the system and act as disturbing elements. A tumor may at first be part of the system (nonautonomous cell multiplication), to degenerate into an autonomous tumor upon further growth. For an autonomous tumor of the effector organ the situation is drawn in Fig. 7. Equation (10) now changes into

$$y_r = cK_c y_e + ax_a, \tag{18}$$

where $x_a$ is the effect of a single *autonomous* cell upon the steady state level of autonomous production and $a$ is the number of autonomous cells. Substitution of (8) and (9) into (18) gives for the regulated state

$$y_r = \frac{K}{1+K} y_i + \frac{1}{1+K} ax_a. \tag{19}$$

The effect of the disturbance $ax_a$ is compensated in the early stages of autonomous growth. The system is completely thrown out of action (decompensated) as soon as

$$ax_a = y_i. \tag{20}$$

Upon further growth the level of the "regulated" state $y_r$ becomes pathologically high [and the original effector may atrophy as a result of its inactivity, an effect that may already start before the condition of (20) has been

reached]. Comparable situations occur upon autonomous growth of other cells.

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