Title: Mathematical Theory of Metabolism and Isotope Kinetics, Especially Using the Analogue Computer for the Analysis of Iodine Metabolism in Thyroid Gland

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MATHEMATICAL THEORY OF METABOLISM AND ISOTOPE KINETICS, ESPECIALLY USING THE ANALOGUE COMPUTER FOR THE ANALYSIS OF IODINE METABOLISM IN THYROID GLAND*

By

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Synopsis

The general theory of mathematics of metabolism, which was developed by Sugita, one of the authors of this paper, relating to the thermodynamical analysis, is reconsidered and a formulation of isotope kinetics is given. As an example the mathematical analysis of iodine metabolism in thyroid gland using I\textsuperscript{131} is tried by Fukuda, co-author of this paper, from the medical point of view. One trial is tested by using analogue computer and the result of the computation is given. For this purpose the system parameters of the differential equations of isotope kinetics must be determined. We have relied upon the consideration of the steady state. It is not possible, however, to determine their values by simple mathematics, so that we assumed some trial values which gave the reasonable result in the steady state as well as in the analogue computation. Analogue computer is best fitted for such a trial and error method. We also have changed some values of the parameters and obtained the curves corresponding to some diseases.

The use of analogue computer may be interesting if we apply it as a simulator of the processes in vivo.

I. Introduction

In the preceding paper\textsuperscript{1} Sugita, co-author, has presented a system of differential equations of the kinetics of the metabolic systems which describes the behaviour of a material labelled by a certain element X, radioactive as well as non-radioactive. The formula can be written in

$$\frac{dn_i(X)}{dt} = \sum_j K_{ij} n_j(X) - \sum_k K_{ki} n_i(X) - K \cdot n_i(X) + I_i(t), \quad (1.1)$$

where \((i)n_i(X)\) is the quantity\textsuperscript{2} per unit volume of this element X at a compartment \(i\), specified by the state of chemical combination as well as local conditions like adsorption at

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\textsuperscript{2} If the compartment is the local one, we consider the quantity per unit volume, i. e. density, although the volume in practice may be very small.
a certain site in the cell structure or of the concentration of some part and (ii) $K_{ji}$ is the transition probability from a compartment to another, for instance from $j$ to $i$, and is the function of the quantities $n_i(X), n_j(Y), \ldots$, and $t$.

$I_i(t)$ is the input function, which is the rate of input of the compounds containing $X$ from the external system directly to the compartment $i$ and $K_{j,i}$ is the probability that those compounds are excreted from $i$ to the outward. If there is no direct transport from $i$ to the external system or vice versa, we put $K_{j,i} = 0$ or $I_i(t) = 0$ respectively.

Therefore, $K_{ji}n_j(X)$ for instance, is the flux of matter from $j$ to $i$. If $j$ and $i$, on the one hand, corresponds to the state of chemical combinations, the flux is the rate of chemical reaction. In this case the flux is the scalar one. On the other, if $i$ and $j$ denotes the state of local conditions like concentration, the flux is vectorial like passive diffusion or active transport.

Qualitatively, interesting results can be obtained from (1.1) which will be mentioned afterwards in IV, but quantitatively, however, the mathematical analysis of the system of the equations (1.1) is very difficult, for the most of the rate constants in vivo are not known or not certain. Some of them are known in enzymatic reactions in vivo or in vitro. However, we are not sure whether their values in vitro are the same as those in vivo or not. Moreover, the variation of their values are very important in considering the mechanism of regulation. So that we must stress the importance of the explicit dependence of $K_{ji}$ or $K_{ki}$ on $t$ as considered above. The theory of the systems having variable rate constants is called by the authors the flexible neck theory, which will be mentioned in II.

The analysis of the respiratory reactions, for instance, was tried by Chance and others using digital computer. They used the knowledge of enzymatic reactions and the mathematical relations like the equation of Michaelis and Menten. Such a method may be a trial and an important step in the study in this field. Only the trial and error method using computer may be the possible way of approach.

In the case of isotope kinetics, however, the analysis is far simpler, because we can rely upon the linear analysis using analogue computer very efficiently, which is most suitable for the method of trial and error.

In this paper we have discussed the mathematics of isotope kinetics basing on the equation (1.1) and then tried the analysis of iodine metabolism in the thyroid gland using the analogue computer at Meiji University.

II. Metabolism in the Steady State

In the case of isotope kinetics also the determination of system parameters is very complicated. If the nature of reactions in the steady state is known, it is helpful for the determination of these constants.

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3 The variation of these probabilities with time is very important in considering the regulation of the metabolic systems. The flexible neck theory is presented by the authors for the analysis of such regulating systems.

4 This flux was written $Q_{ji}$ in the previous paper.


Let us simplify (1.1) at first in considering that all the input functions other than $I_0$ are zero, i.e.
\[ I_0 \neq 0, \quad I_i = 0 \quad (i = 1, 2, \ldots, n) \]
and also that all the probability $K_i$ other than $K_u = L$ are zero, i.e.
\[ K_i = 0 \quad (i = 0, 1, \ldots, n - 1), \quad K_u = L. \]

Then we have
\[
\begin{align*}
dn_0(X)/dt &= \sum_j K_{j0} n_j(X) - \sum_k K_{k0} n_k(X) - I_0(X), \\
dn_i(X)/dt &= \sum_j K_{j,i} n_j(X) - \sum_k K_{k,i} n_k(X) \\
dn_u(X)/dt &= \sum_j K_{j,u} n_j(X) - \sum_k (K_{k,u} + L) n_k(X)
\end{align*}
\]

In the steady state $dn_i(X)/dt = 0$ and
\[ \sum_j K_{j,j} n_j(X) = \sum_k K_{k,k} n_k(X) \quad (2.2) \]

This relation corresponds to the evidence of the metabolic turnover and shows that the steadiness is maintained by the compensation of fluxes like $\sum_j K_{j,j} n_j(X)$ and $\sum_k K_{k,k} n_k(X)$, where $n_j(X)$ and $n_k(X)$ are the steady state values of $n_i(X)$ and $n_n(X)$ respectively and will be used in determining the system parameters of isotope kinetics in III.

Again from (2.1) we have
\[ \Sigma_i d n_i(X)/dt = I_0(X) - Ln_n(X). \quad (2.3) \]

Therefore, applying the step function of the type
\[ I_0(t) = I_0 = \text{const}, \quad \text{for} \quad t < 0 \]
and
\[ I_0 = 0 \quad \text{for} \quad t \geq 0, \]
we have
\[ \frac{d}{dt} (\Sigma_i n_i(X)) = -Ln_n(X) \quad (2.3') \]
for $t \geq 0$. While $n_n(X) = \Sigma n_i(X)$, so that
\[ \frac{d}{dt} (\Sigma_i n_i(X)) \leq -L(\Sigma n_i(X)). \quad (2.3'') \]

If instead of applying step input, $I_0(t) = I_0$ is assumed as constant and the system is in the steady state, then
\[ \frac{d}{dt} (\Sigma_i n_i(X)) = I_0 - Ln_n(X) = 0 \quad (2.4) \]
and
\[ \dot{n}_n(X) = I_0/L. \quad (2.5) \]

Meanwhile, although $I_0$ is constant, the system is not necessarily in the steady state. Let us consider an instance of such systems, in which $n_i(X)$'s are nearly equal to the steady state values and fluctuating in the manner
\[ n_i(X) = \bar{n}_i(X) + \Delta_i \quad (2.6) \]

Then from (2.1) we have

\[ \frac{d\Delta_i}{dt} = \sum_{k=0}^{n} A_{ik} \Delta_k, \quad (i = 0, 1, \ldots, n), \quad (2.7) \]

where \( A_{ik} \)'s are the expansion coefficients of the right of (2.1) with respect to \( \Delta_k \) and determined by the quantities like \( K_{ik} \)'s and \( \frac{\partial}{\partial n_i(X)} K_{ik} n_i(X) \), so that they are the functions of the steady state values of \( n_i(X) \)'s.

In some cases (2.7) shows small oscillation of \( \Delta_i \)'s which means the pulsation of the metabolic fluxes for the constant input of \( I_0 \). In this respect (2.7) is different from (3.1) of the isotope kinetics of III.

An instance of such a pulsation is given by

\[ \frac{dn_0}{dt} = I_0 - (k_1 n_1) n_0 \quad (2.8') \]

and

\[ \frac{dn_1}{dt} = k_1 n_1 n_0 - k_2 n_1 \]

where \( k_1 \) is the rate constant of the transport from 0 to 1 and the reaction is auto-catalytic, while \( k_2 \) is the rate constant of the reaction of the first order. If we put

\[ n_i = \bar{n}_i + \Delta_i \]

in (2.8), then we have the equation of small oscillation:

\[ \frac{d\Delta_0}{dt} = -a_{11}\Delta_0 - a_{12}\Delta_1, \quad (a_{11} = k_1 \bar{n}_1, \ a_{12} = k_1 \bar{n}_0) \quad (2.8') \]

and

\[ \frac{d\Delta_1}{dt} = a_{21}\Delta_0 \quad (a_{21} = k_1 \bar{n}_1), \]

where \( a_{12} = k_1 \bar{n}_0, \ a_{11} = a_{21} = k_1 \bar{n}_1 \). Applying the Laplace transformation we have

\[ M(\hat{\Delta}_0) = 0, \quad M = \begin{pmatrix} (a_{11} + s, a_{12}) \\ -a_{21}, s \end{pmatrix} \]

where \( \hat{\Delta}_0 \) and \( \hat{\Delta}_1 \) are the Laplace transformation of \( \Delta_0 \) and \( \Delta_1 \) respectively and \( M \) is the matrix specifying the equation (2.8'), which is different from the metabolic matrix introduced by Fukuda because the characteristic equation determined by the matrix \( M \) gives the oscillating or pulsating deviation from the steady state (see III).

Ordinarily open system is believed to attain the stationary state, in which the entropy production is the minimum. Nevertheless, it is not the case when pulsating flow of matter is realized. Also Sugita, co-author, has professed that the state of the maximum velocity of free energy consumption may be realized. These theories or hypothesis must be reconsidered from the viewpoint of the flexible neck theory.

III. Mathematics of Isotope Kinetics

Let us assume that the system is in the steady state and that the percentage of the compound labelled by the radioactive isotope is very small. Then we have from (2.1)\(^{12}\)

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12 \( Q_H \) of the previous paper corresponds to \( K_i, n_i \) (X) of (3.1).
\[
\begin{align*}
\frac{dx_0}{dt} &= \sum_k k_{0k} x_j - \sum_k k_{0k} x_0 + t_0, \\
\frac{dx_i}{dt} &= \sum_k k_{ik} x_j - \sum_k k_{ik} x_i, \\
\frac{dx_n}{dt} &= \sum_k k_{jn} x_j - \sum_k (k_{nk} + L) x_n,
\end{align*}
\]

where \(k_{ik}\)'s are different from \(A_{ik}\) of (2.7), for the system is in the steady state, so that

\[
\frac{\partial}{\partial n_j(x)} k_{ik} n_i(x) = 0.
\]

In this case \((k_{1n_1})\) of (2.8), for instance, is constant in the steady state, while it is not for the pulsating deviation of (2.8').

Applying the Laplace transformation we have

\[
\begin{align*}
-(\sum_k k_{0k} + s) \dot{x}_0 + \sum_j k_{jk} \dot{x}_j &= -I(s), \\
-(\sum_k k_{ik} + s) \dot{x}_i + \sum_j k_{ij} \dot{x}_j &= 0, \\
-(\sum_k k_{nk} + L + s) \dot{x}_n + \sum_j k_{jn} \dot{x}_j &= 0,
\end{align*}
\]

or

\[
\begin{align*}
\dot{x}_0 &= \sum_k M_{0k}(s) \dot{x}_j + \frac{I(s)}{\sum_k k_{0k} + s}, \\
\dot{x}_i &= \sum_k M_{ik}(s) \dot{x}_j, \quad (i = 0, \ldots, n),
\end{align*}
\]

where

\[
M_{0k} = \frac{k_{0k}}{\sum_k k_{0k} + s}, \quad M_{ik} = \frac{k_{ik}}{\sum_k k_{ik} + s}, \quad M_{jn} = \frac{k_{jn}}{\sum_k k_{nk} + L + s}
\]

are the components of the so-called metabolic matrix, and \(\dot{x}_0, \dot{x}_i, \dot{x}_n\), and \(I(s)\) are the Laplace transformation of each respective quantity, i.e.

\[
\dot{x}_i = \int_0^\infty x_i(t) e^{-st} dt.
\]

If we apply the input pulse \(i(t)\) having the pulse height \(q\) and time duration \(\tau\), which is very small, then the Laplace transformation of \(i(t)\) is given by

\[
I(s) = \frac{q}{s} (1 - e^{-s\tau}) = q \tau,
\]

which gives the injected quantity. Let us assume that this value is 1, so that we put \(I(s) = 1\) in (3.2). Then using the mathematical formula

\[
\lim_{t=\infty} x_i(t) = \lim_{s=0} (s\dot{x}_i(s)),
\]

the value of \(x_i(t)\) at very large \(t\) after the input pulse at \(t=0\) is given by

\[
x_i(\infty) = \sum_k M_{ik}(s) x_k(\infty).
\]

These values \(x_i(\infty)\) must tend to zero from the physical point of view. Therefore, the metabolic matrix must satisfy the following condition

\[
\| \delta_{ik} - M_{ik} \| \neq 0, \quad (i, k = 0, 1, \ldots, n),
\]

where \(\delta_{ik} = 0\) for \(i \neq k\) and \(\delta_{ik} = 1\) for \(i = k\). The physical meaning of this condition is now in consideration. It is also required that \(x_i(t) \geq 0\). Whether we can meet such a requirement as a mathematical consequence of (3.1) or not is not clear at present.
If the condition (3·8) is satisfied, the steady state value of \( x_i(t) \) for the constant input \( i_0 \) is given by

\[
\begin{align*}
\dot{x}_0 &= \sum_j M_{ji} \dot{x}_j + \frac{1}{\sum_k h_{0k}}, \\
\dot{x}_i &= \sum_j M_{ji} \dot{x}_j, \quad (i:1, 2, \ldots, n)
\end{align*}
\]  

(3·9)

where we have put \( i_0 = 1 \) for simplicity. Here, we are considering not only the steadiness with respect to \( n_i(X) \), the total quantity, but also with respect to \( x_i \), the small quantity of isotope. Then we can readily see that the ratio of the steady state values of \( x_i \) is equal to that of \( n_i(X) \) of \( \Pi \), i.e.

\[
\dot{x}_0 : \dot{x}_1 : \ldots : \dot{x}_n = \dot{n}_0(X) : \dot{n}_1(X) : \ldots : \dot{n}_n(X)
\]  

(3·10)

This relation (3·10) is intuitively clear if the frequency of metabolic turnover is large enough, because the percentage of the compounds labelled by the isotope must be constant throughout the compartments, which are found in the steady state.

Therefore, if the ratio of these \( \dot{n}_i(X) \) is known, we can determine the components of the matrix of metabolism, \( M_{ji} \), and the system parameters \( K_{ji} \) too.

As metabolism in the organism is greatly complicated, the phenomenological way of thinking seems to be useful. Our equation (3·1) can be assumed at first considering transitions between every compartment phenomenologically. Then the probabilities, \( K_{ji} \), may be determined by the trial and error method. For such a method the use of analogue computer is most fitted. Nevertheless, their determination is not easy and sometimes troublesome if the number of parameters which must be determined is large. Therefore, the steady state consideration is very useful for the determination of the system parameters, \( K_{ji} \)’s.

IV. Iodine Metabolism in Thyroid Gland

Since the metabolism in this gland also is very complicated, we adopt a phenomenological way of thinking and as a trial Fukuda, co-author, has schematized the processes as shown by Fig. 1, considering the recent developments of researches in this field. In Fig. 1 iodine is taken into the thyroid follicle by active transport and incorporated into tyrosine of globulin molecules in the epithelial cells, in which \( M^\alpha, D^\alpha, T_3^\alpha, \) and \( T_4^\alpha \) are formed (see Table I). This is one of our fundamental assumptions which is likely ascertained by the analogue computation (see V). The macro-molecules labelled by these amino-residues diffuse into the thyroid follicle with the rate constant \( k^i \). Then the mutual conversion of \( M, D \), and others is assumed to be inactivated, so that the notation \( i \) is assigned to \( M, D \), and others. By enzymatic action \( M^\alpha, D^\alpha, T_3^\alpha, \) and \( T_4^\alpha \) are liberated from inactivated thyroglobulin. Then \( M^\alpha \) and \( D^\alpha \) are deiodinated enzymatically and the iodine thus liberated is reused (so-called “intra-thyroidal iodine cycle”). The iodothyronines thus liberated (\( T_3^h \) and \( T_4^h \)) are loosely bound to “thyroxine binding protein (TBP)” and released into the circulating blood. The quantity of \( ^{131}I \) (corresponding to radioactivity of this isotope) in a compartment \( i \) is \( x_i \), of which \( x_3, x_4, x_5, \) and \( x_6 \) are listed in the following table:
Considering the process \( x_j \rightarrow x_i \), we take in general that \( j \) is smaller than \( i \), and the transitions \( j \rightarrow i \) in which \( j \) is greater than \( i \) are neglected except those \( x_3^h, x_4^h \rightarrow x_1 \) and \( x_1 \rightarrow x_0 \). The latter, however, is considered only in the case shown by fig. 16, so that \( k_1' \) is usually put as \( k_1' = 0 \). Also the transition from a compartment to those other than the next one is neglected except those \( x_2 \rightarrow x_3, x_3 \rightarrow x_5 \), and \( x_4 \rightarrow x_6 \). In the exceptional cases we have the branched transitions like \( x_2 \rightarrow x_3, x_2 \rightarrow x_4 \). Thus in the steady state (with respect to total iodine) we have the following linear differential equations of 17 variables (\( x = dx/dt \)):

\[
\begin{align*}
\dot{x}_0 &= -(k_0 + k_0')x_0 + k_1'x_1 + I_0, \\
\dot{x}_1 &= -(k_1 + k_1')x_1 + k_0x_0 + k_0^O(x_3^h + x_4^h), \\
\dot{x}_2 &= -(k_2 + k_2')x_2 + k_1x_1, \\
\dot{x}_3 &= -(k_3 + k_3' + k_3^h)x_3 + k_2x_2, \\
\dot{x}_4 &= -(k_4 + k_4' + k_4^h)x_4 + k_3x_3 + k_3^h, \\
\dot{x}_5 &= -k^h_3x_5 + k_3'x_3 + k_3x_4, \\
\dot{x}_6 &= -k^h_4x_6 + k_4x_4,
\end{align*}
\]

where \( i_0 \) is the input function. It is clear that the conditions of (3·8) and of \( x_i \geq 0 \) are satisfied. An intuitive model of these rate processes using tank and fluid is given by Fig. 2.

For the estimation of the system parameters, \( k_i \), we took the state of isotope kinetics into consideration. If every steady state value of \( x_i \) (with respect to the isotope quantity) was known, the system parameters, \( k_i \)'s, could be determined by using the relation (3·9). Such a simple mathematics, however, cannot be available in our case. Only the method of
From (4·3) and (4·5) we have one of the important relations

$$\sum_{n=3}^{6} \bar{x}_n i = \frac{k_1}{k_h} \bar{x}_1.$$  \hspace{1cm} (4·6)

From (3·10) and the observations concerning the metabolism of the net iodine, radioactive as well as non-radioactive, we can assume the reasonable value of the ratio

$$\bar{x}_1 / \sum_{n=3}^{6} \bar{x}_n i = \frac{n_1(I_2)}{\sum_{n=3}^{6} n_1(I_2)} = 1/100,$$

Therefore, from (4·6) we will take the ratio

$$k_h = 0.01 k_1$$  \hspace{1cm} (4·7)

as the round number approximation.

Again, from (4·1) we have in the steady state

$$\bar{x}_1 = -(k_1 + k_{1i}) \bar{x}_1 + k_0 \bar{x}_0 + k^D (\bar{x}_3 + \bar{x}_4) = 0$$

$$\therefore (k_1 + k_{1i}) \bar{x}_1 - k_0 \bar{x}_0 + k^D (\bar{x}_3 + \bar{x}_4) = 0.$$  \hspace{1cm} (4·8)

Meanwhile,

$$\bar{x}_n h = h^b \bar{x}_n i -(h^D + h^b) \bar{x}_n h = 0, \quad (n = 3, 4)$$

trial and error may be the possible way of approach, although the steady state consideration is very helpful.

Henceforth, let us give the steady state consideration. From (4·1) we have in the steady state (with respect to the isotope quantity)

$$\bar{x}_2 = k_1 \bar{x}_1 - (k_2 + k_{2i}) \bar{x}_2 = 0$$

$$\therefore (k_2 + k_{2i}) \bar{x}_2 = k_1 \bar{x}_1.$$  \hspace{1cm} (4·2)

Meanwhile, adding both sides of (4·1) pertaining to $x_3$, $x_4$, $x_5$, and $x_6$ to each other, we have

$$x_3 + x_4 + x_5 + x_6 = (k_2 + k_{2i}) \bar{x}_2$$

$$- k^i (x_3 + x_4 + x_5 + x_6),$$

so that in the steady state

$$(k_2 + k_{2i}) \bar{x}_2 = k^i (\sum_{n=3}^{6} x_n) = k_1 \bar{x}_1$$  \hspace{1cm} (4·3)

Again, from (4·1) pertaining to $x_3 i$, $x_4 i$, $x_5 i$, and $x_6 i$ we have

$$\bar{x}_n i = k^i \bar{x}_n - k_h \bar{x}_n i = 0$$  \hspace{1cm} (n = 3, 4, 5 and 6)  \hspace{1cm} (4·4)

in the steady state. Then

$$\bar{x}_n i = \frac{k^i}{k_h} \bar{x}_n$$  \hspace{1cm} (4·5)

From (4·3) and (4·5) we have one of the important relations

$$\sum_{n=3}^{6} \bar{x}_n i = \frac{k_1}{k_h} \bar{x}_1.$$  \hspace{1cm} (4·6)

Again, from (4·1) we have in the steady state

$$\bar{x}_1 = -(k_1 + k_{1i}) \bar{x}_1 + k_0 \bar{x}_0 + k^D (\bar{x}_3 + \bar{x}_4) = 0$$

$$\therefore (k_1 + k_{1i}) \bar{x}_1 = k_0 \bar{x}_0 + k^D (\bar{x}_3 + \bar{x}_4).$$  \hspace{1cm} (4·8)

Meanwhile,

$$\bar{x}_n h = h^b \bar{x}_n i -(h^D + h^b) \bar{x}_n h = 0, \quad (n = 3, 4)$$
in the steady state, so that
\[(k^D + k^L) \cdot (\dot{x}_3^h + \dot{x}_4^h) = k^b (\dot{x}_3^h + \dot{x}_4^h). \quad (4.9)\]

From (4.6) and (4.9) we have in cancelling \(k^b\)
\[k^D (\dot{x}_3^h + \dot{x}_4^h) = x \frac{\dot{x}_3^h + \dot{x}_4^h}{\sum_{n} \dot{x}_n^i}, \quad (4.10)\]
where
\[x = \frac{k^D}{(k^D + k^L)}. \quad (4.11)\]

Therefore, from (4.8) and (4.10) we have
\[(k_1 + k_1^{'}) F^{-1} \ddot{x}_1 = k_0 \ddot{x}_0, \quad (4.12)\]
where
\[F^{-1} = 1 - x \frac{\dot{x}_3^h + \dot{x}_4^h}{\sum_{n} \dot{x}_n^i}, \quad (4.13)\]
The observation of the ratio of \(\ddot{x}_0(I_2)\) and \(\ddot{x}_1(I_2)\) shows \(1/10\) as the round number approxima-
tion, so that we will assume the value
\[\ddot{x}_1 = 10 \ddot{x}_0 \quad \text{and} \quad \frac{k_0}{k_1 + k_1^{'}} F = 10. \quad (4.14)\]
The approximate ratio of \(\ddot{x}_3^h(I_2), \ddot{x}_4^h(I_2), \ddot{x}_5^h(I_2), \) and \(\ddot{x}_0(I_2)\) is known as
\[
\ddot{x}_3^h: \ddot{x}_4^h: \ddot{x}_5^h: \ddot{x}_6^h = \ddot{x}_3^h(I_2): \ddot{x}_4^h(I_2): \ddot{x}_5^h(I_2): \ddot{x}_6^h(I_2) = 40:47:2:12,
\]
then
\[\frac{\ddot{x}_3^h + \ddot{x}_4^h}{\sum_{n} \dot{x}_n^i} = \frac{87}{101}. \quad (4.15)\]
If we put on the one hand \(k_1' = 0\) and \(k^L = 0,\)
then
\[F^{-1} = 1 - \frac{87}{101} = \frac{13}{101}\]
and
\[\frac{k_0}{k_1} F = \frac{k_0}{k_1} \cdot \frac{101}{13} = 10.
\]
Therefore, the round number approximtion of \(k_0\) is
\[k_0 = k_1. \quad (4.16)\]
On the other, if we put \(k_1' = 0, k^L = 0\) and assume the value
\[\alpha = \frac{k^D}{k^D + k^L} = \frac{4}{5}\]
as a trial, then
\[F^{-1} = 1 - \frac{348}{505} = \frac{157}{505}\]
and

$$k_0 = 10F^{-1}k_1 = \frac{1570}{505}k_1. \quad (4.18)$$

Then the round number approximation of $k_0$ can be written

$$k_0 = 3k_1.$$

From Figs. 1 and 2 let us take the following reaction equations:

$$\begin{align*}
II + T_y & \overset{k_2}{\longrightarrow} (M^a)^*, \\
II + M^a & \overset{k_3}{\longrightarrow} (D^a)^*, \\
I_2 + (M^a)^* & \overset{k_3}{\longrightarrow} (D^a)^*, \\
(M^a)^* + D^a & \overset{k_3}{\longrightarrow} (T^a)^*, \\
M^a + (D^a)^* & \overset{k_3}{\longrightarrow} (T^a)^* 
\end{align*}$$

and

$$\begin{align*}
(M^a)^* + D^a & \overset{k_3}{\longrightarrow} (T^a)^*, \\
M^a + (D^a)^* & \overset{k_3}{\longrightarrow} (T^a)^* 
\end{align*}$$

into consideration, the we can assume that

$$k_3' = k_4', \quad k_2 = k_3', \quad \text{and} \quad k_3 = k_3.$$  \quad (4.19)

From (4.1) and (4.5) we have the relations

$$\frac{\tilde{x}_4}{\tilde{x}_6} = \frac{\tilde{x}_4}{\tilde{x}_3} = k_4 = \frac{12}{47} \quad \therefore \quad k_3 = 4k_4, \quad (4.20)$$

$$\frac{\tilde{x}_3}{\tilde{x}_6} = \frac{\tilde{x}_3}{\tilde{x}_5} = \frac{k_3 + k_3' + k_4}{k_3 + k_3' + k_4} = \frac{47}{40}, \quad (4.21)$$

$$\frac{\tilde{x}_5}{\tilde{x}_6} = \frac{\tilde{x}_5}{\tilde{x}_4} = \frac{k_3' + k_4'}{k_3' + k_4'} = \frac{k_3' + k_4'(\tilde{x}_3/\tilde{x}_3)}{k_4'(\tilde{x}_3/\tilde{x}_3)} = \frac{k_3' + k_4'(47/40)}{k_4'(47/40)} = \frac{1}{6}. \quad (4.22)$$

Then, from (4.19) and (4.22) we have the round number approximation of $k_3'$ and $k_3'$

$$k_3' = k_3' = \frac{1}{10}k_4 \quad (4.23)$$

and from (4.21)

$$\left(1 + \frac{k_3}{k_3 + k_3' + k_4'} \right) \frac{k_3 + k_3' + k_4'}{k_3 + k_3' + k_4'} = \frac{47}{40},$$

and from (4.19) and, (4.20), and (4.23) we have

$$\frac{k_3 + k_3' + k_4'}{k_4 + k_3' + k_4'} + \frac{k_3}{k_4 + k_3' + k_4'} = \frac{2k_3 + 4.1k_4}{5.1k_4} = \frac{47}{40} \quad \therefore \quad \frac{k_3}{k_4} = \frac{5.1}{2} \left(\frac{47}{40} - \frac{4.1}{5.1}\right) = 1.$$

Therefore, the round number approximation of $k_4$ is

$$k_4 = k_3. \quad (4.24)$$

Considering these relations (4.7), (4.16) or (4.16'), (4.19), (4.22), (4.23) and (4.24) and assuming $k_1' = 0$, we can put

\[\text{\footnote{I} and ( ) are the radioactive one. The quantity of I is very small and can be neglected.}\]
In the latter case we put temporarily
$$k^D = 40 \quad \text{and} \quad k^L = 10$$
as the plausible values. Then from those round number approximation values we can compute the following reasonable values
$$\bar{x}'_1 = 39.25 \bar{x}, \quad \bar{x}'_2 = 46.67 \bar{x}, \quad \bar{x}'_3 = 2.15 \bar{x}, \quad \bar{x}'_4 = 11.67 \bar{x},$$
and
$$\bar{x}_1 = 9.65 \bar{x}.$$We are not sure at present of the data for the determination of \(k^R\), so that we will put temporarily
$$k^R = 10 \bar{k}_1.$$For the determination of \(k^E\) we will use the relation
$$\bar{x}'_3 + \bar{x}'_6 = \frac{k^R}{k^E} (\bar{x}^3 + \bar{x}^6) = \frac{k^h}{k^E} (\bar{x}^3 + \bar{x}^6) = \frac{k^h}{k^E} \left( \sum_{n=3}^{6} \bar{x}^n, - \bar{x}^3 - \bar{x}^6 \right).$$From (4.6) and (4.13) we have
$$\bar{x}'_3 + \bar{x}'_6 = \frac{k_0}{k^E} \left( 1 - \frac{1}{\alpha} \frac{k_1 + k_1'}{k_1} F - \frac{F - 1}{k_1} \right) k_1 F k_0$$
$$= \frac{k_0}{k^E} \left( F - \frac{1}{\alpha} \frac{k_1 + k_1'}{k_1} (F - 1) \right) \frac{k_1}{k_1 + k_1'} \bar{x}_0.$$This is the third important relation.
If we assume the values \(k_1' = 0\), \(\alpha = 4/5\) and
$$k^E = 0.3 \bar{k}_1$$then from (4.18) we can calculate the reasonable value:
$$\bar{x}'_3 + \bar{x}'_6 = 4.77 \bar{x}_0.$$The determination of these values for the system parameters are but a trial, so that it is desirable to test other possibilities. However, we did not have time enough to test them. In future such a test will be done using analogue computer.

V. Use of Analogue Computer

We used the analogue computer at the Meiji University through the kind understanding of Prof. Jinbo of that University. The operation was done by Mr. Hirabara, a student of the graduate course, under the direction of Mr. Ogawa, a member of Prof. Jinbo's laboratory. The block diagram is given by Fig. 3.
in which we have put $k'_1 = 0$. In the case of $k'_1 \neq 0$, the block diagram is different from that of Fig. 3.

In the case of $k'_1 = 0$ we have solved, instead of applying the input pulse $I_i(t)$, another analogue circuit, the solution of which is

$$x_0 = Qe^{-(k_3 + k'_3)t}$$  \hspace{1cm} (5.1)

and the output $x_0$ is applied as the input. $Q$ of (5.1) corresponds to the injected quantity of $\text{I}^{131}$. 

The photographs of the curves obtained are reproduced in the figures from 4 to 19, where the height of the curves does not represent the computed value (CV), because the gain of the transfer functions of Fig. 3 are modified for the benefit of computation. So that the note like CV: 3/8 is written, showing that the computed or true value is 3/8
times the apparent height of the curves. The pen recorder magnification is written in the manner PRM: 4, for instance.

$x_1$ of Fig. 4 shows a sharp peak, while the peak of the pulse of (5·1) is too steep, so that it cannot be expressed as a curve having the breadth in this time scale. The interval of the time marks is 1 sec, and that of the Fig. 4b is 5 times enlarged compared with that of Fig. 4a. The upper and the lower curves of the same graph paper are recorded at the same time. The step curve of the lower is the input to get the output $x_0$ of (5·1), the height of which is $Q$.

The sharp peak of $x_3$ or $x_4$ of Fig. 5 is similar to that of $x_1$. However, CV is the small quantity of 1/100, so that their height is about 1/100 of that of $x_1$. This is why those compounds M and D cannot be found in the epithelial cells, although the incorporation of I₂ is assumed in these cells. If we look at the level of the tank of Fig. 2 having large $k_j$, it is very much lower than that of the tank having small $k_j$. For the same reason, the $x$ of the compartment which shows a sharp peak or short life, must be very small so that it cannot be detected in some cases experimentally. For this reason I₂ was considered formerly as being incorporated in some places other than in the epithelial cells. However, our computation shows that Fukuda's opinion concerning the I₂ incorporation is justified.

Fig. 6 shows the relation between $x_1$ and $x_3'$. The curve of $x_3'$ does not show a sharp peak like that of $x_1$. In Fig. 6a, $k_0=3$, in Fig. 6b, however, $k_0=1$ and the peak of $x_1$ is somewhat higher than that of Fig. 6a. The time scale of Fig. 6c is 5 times enlarged compared with that of Fig. 6a or 6b.

The curves upper and lower of Fig. 7a and 7b show that of $x_3'$ and $x_4'$ respectively. The upper curves of Fig. 8a and Fig. 8b show that of $x_3'$, and the upper one of Fig. 9a and 9b show that of $x_6'$. The time scale of the figs 7b, 8b, 9b is enlarged by 5 times of that of figs 7a, 8a, and 9a.

We can see in these curves that $x_3'$ has almost the same height as that of $x_1$ and also that $x_4'>x_3'$ as is expected. The height of $x_6'$ is about 1/4 of that of $x_4'$ (see fig.11). Meanwhile the height of $x_5'$ is only about 1/5 of that of $x_6'$. These results are reasonable if

Fig. 5
we compare them with observations. Fig. 8a (lower) and Fig. 8b (lower) show the curve of $x_5^c$ and Fig. 9a (lower) and fig. 9b (lower) that of $x_6^c$. The height of $x_5^c$ is about 1/100 of $x_1$ and that of $x_6^c$ is about 1/1000 of $x_1$. These results also are not very different from that of observations. The time interval of fig. 10b is 5 times that of fig. 10a.

The curves of fig. 11a (upper) are recorded at the same time with the input step, showing that the time lag can be observed for the initial ascension of the curve of $x_5^c$. The curves of Fig. 11b for $x_3^i$ do not show such a noticeable time lag. $k_0=0.1$ for the fig.s 11, 12 and the curve of fig. 12a corresponds to that of fig. 6a and 6b and fig. 12b to that of fig. 6c. The value of $k_0=0.1$ corresponds likely to the case of a small animal but the value of $k_0'=3$ does not fit into such an animal. Therefore, this is likely to be in the case of the disease (hypofunction) of man. The curve of fig. 13a corresponds to that of 10a and that of fig. 13b to that of fig. 10b. The upper curve of fig. 13c corresponds to that of $x_5^c$ and the lower to that of $x_6^c$. In both cases PRM: 4.

The figs. from 14 to 17 show the uptake curve of the thyroid gland, which are recorded by summing up the outputs of $x_1$, $x_3^i$, $x_4^i$, $x_5^i$, and $x_6^i$. The time interval of these figures assigned by a is 1/5 of the normal one and those by b is 5 times enlarged.

We have taken the value $k_0=3$ for the figures from 4 to 19 except those of figs 6b and 6c. $k_0=1$ for figure 10 and for figures from 14 to 16, the former value is too high for normal Japanese. So that we have taken the value $k_0=1$. Then the maximum uptake value can be estimated to be about 20% coinciding to the value of normal Japanese. The curves of the case of $k_0=0.1$ is listed as references. $k_0=1$ for curves of the figs. 14 to 16. In fig. 14 $k^h=0.01$, $k^l=0$. In fig. 15 $k^h=0.1$, $k^l=0$; in fig. 16 $k^h=0.01$ and $k^l'=3$. $k^l'=5$, PRM: 2 for the step input of all these curves. In fig. 15 we have assumed
Fig. 7a and 7b. \( k_0 = 3, k_1 = 1/100, k_1' = 0, k_1' = 3, \) CV: 2, PRM: 10

Fig. 8a and 8b. \( k_0 = 3, k_1 = 1/100, k_2' = 0, k_2' = 3, \) CV: 1/20, CV: 1/600 for \( x_5^1 \), CV: 1/600 for \( x_5^2 \), PRM: 4 for both curves.

Fig. 9a and 9b. \( k_0 = 3, k_1 = 1/100, k_2' = 0, k_2' = 3, \) CV: 1/2, CV: 1/100 for \( x_6^1 \), CV: 1/100 for \( x_6^2 \), PRM: 4 for both curves.
Fig. 10a and 10b. $k_5=1$, CV: 2 for $x_t^4$, CV: 1/2 for $x_t^4$, PRM: 4 for both curves.

Fig. 11a and 11b. $k_4=0.1$, PRM: 2 for pulse input and PRM: 4 for $x_t^4$ and $x_t^6$.

Fig. 12a and 12b. $k_3=0.1$, $k^4=1/100$, Fig. 12a corresponds to 6a and 12b to 6c.
Fig. 14a and 14b. \( h_i = 1, \; h^* = 1/100, \; k_{i'} = 0, \; k_{i''} = 3, \) PRM: 20 for the lower curve and PRM: 2 for the step input. CV: 1/8 for \( x_i \) and the others are referred to \( x_1 \). The time interval of the curve a is the normal one and that of b is 25 times the normal.

Fig. 15a and 15b. \( h_i = 1, \; h^* = 1/10, \; k_{i'} = 0, \; k_{i''} = 3, \) PRM: 20 for the lower curve and PRM: 2 for the step input. CV: 1/8 for \( x_i \) and the others are referred to \( x_1 \). The time interval of the curve of a is the normal one and that of b is 25 times the normal.

Fig. 17. \( h_i = 3, \; k_{i'} = 3, \; h^* = 1/10, \; k_{i'} = 0, \) PRM 20: for the uptake curve and PRM: 2 for the input pulse. The time interval is the same with that of Fig. 15b.
Fig. 13a, 13b and 13c. $k_a = 0.1$, PRM: 4. Fig. 13a corresponds to 10a and 13b to 10b. The upper curve of Fig. 13c is that of $x_5^*$ and the lower that of $x_6^*$.

Fig. 16a and 16b. $k_a = 1$, $k_b = 1/100$, $k_{i'} = 3$, $k_{i'} = 5$, PRM: 10 for lower curve and PRM: 2 for the step input. The time interval of the curve a is the normal one and that of b is 25 times the normal.
the large value of $k^h=0.1$ for the rate of hydrolysis. Then the computed curve shows a steep descend. $k_l'=0$ for all curves except the fig. 16. In fig. 16 we took the value of $k_l'=3$. In this case we took the value of $k_0'=5$ by some mistake for the adjustment of the computer. An initial peak and the following plateau of the curve is noticeable.

Fig. 17 corresponds to that of fig. 15b except the value of $k_0=3$. The curve of fig. 18a shows that of $x_6'$ and that of fig. 18b that of $x_4'$ in the case of $k_0=1$ and $k^h=0.1$. Fig. 19a shows the curve of $x_6'$ and Fig. 19b that of $x_6'$. Both curves show steep descend of the curve compared with those of figs. 8 and 10.

The curves of the figures from 14 to 17 was recorded summing the computed values (CV) of the output corresponding to these curves (the curve or $x_5'$ was not recorded at that time).
VI. Discussion and Comment

The mathematical analysis of today is changed in such a way that the computation from the start is a trial instead of the old way in which the starting equations as well as the parameters or numerical data are already verified by experimental basis. This is the way of analysis in the age of electronic computer. From the view-point of the old fashioned theorist, our assumption may probably be a careless one or may lack sufficient experimental basis. However, in our case computations themselves give such basis. If the results are verified as reasonably, then the assumption must be considered as verified empirically. Therefore, we are not always computing basing on sufficiently ensured fundamental equations but in many cases searching or synthesizing such equations so that they give the reasonable results. There are still conservative biologists or medical scientists suspicious of the use of computer analysis, and will not accept the modern way of thinking of such a trial. The biology in future, however, must be extended using analogue as well as digital computer.

Fukuda, co-author, delivered our results at the meeting of the endocrinological society held at Osaka this April, which brought to the attention of some of the members proposing to study this problem experimentally to consider whether it can be confirmed empirically or not. We also are intending to repeat our computation and to use digital computer in the case when the analogue computer does not give accurate data.

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