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# OPTIMAL CONTROL IN LIVER KINETICS

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**Abstract**

We solve a minimization problem in liver kinetics posed by Bass, *et al.*, in this journal, (1984), pages 538–562. The problem is to choose the density functions for the location of two enzymes, in order to minimize the concentration of an intermediate form of a substance at the outlet of the liver. This form may be toxic to the rest of the body, but the second enzyme renders it harmless. It seems natural that the second enzyme should be downstream from the first. However, we can show that the minimum problem is sometimes solved by an overlap of the supports of the two density functions. Even more surprising is that, for certain forms of the kinetic functions and high levels of transformation of the first enzymatic reaction, some of the first enzyme should be located downstream from all the second enzyme. This suggests that the first reaction should be relatively slow.

## 1. Introduction

Bass *et al.* [1] have considered an optimal process consisting of a two-step enzymatic transformation in the liver. This process is defined in terms of two liver kinetic functions. The exact form of the first kinetic function is irrelevant to the problem. However, the form of the second function is critical to the process. Bass *et al.* in [1] were able to solve the optimal control problem when this kinetic function is monotone, and showed that a different strategy is required in the non-monotone case. It is the purpose of this paper to completely solve the problem for all kinetic functions. For a complete and excellent description of the

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physical model see [1]. We shall briefly discuss the import of our results in the last section of this paper.

## 2. The problem

The specific mathematical problem to be solved is to minimize $x(L)$ when

$$x(t) = \varphi(t) - \int_0^t g(s)\beta(x(s))\,ds \tag{1}$$

where the standard assumptions are that

(i) $\beta(0) = 0$, $\beta(x) > 0$ for $x > 0$ and $\beta$ is Lipschitz;

(ii) $\varphi(0) = 0$, $\varphi(L) = \lambda$ and $\varphi$ is absolutely continuous and non-decreasing on $[0, L]$; and

(iii) $g \geqslant 0$, integrable and $\int_0^L g(s)\,ds = 1$.

The functions $\varphi$ and $g$ are to be considered as the controls.

Bass, Bracken and Vyborny [1] considered the case when $\beta$ is strictly increasing. Their result is reproduced here as Theorem 0.

THEOREM 0. *Assume that $\beta$ is non-decreasing on $[0, \lambda]$. An extremal for the minimization problem is obtained by taking any point $t_0 \in (0, L)$; defining $g = 0$ on $[0, t_0]$ with $g$ selected on $[t_0, L]$ to have $\int_0^L g(s)\,ds = 1$; and letting $\varphi$ be an arbitrary function satisfying (ii) such that $\varphi(t) \equiv \lambda$ on $[t_0, L]$. If $\beta$ is strictly increasing, these are the only extremals. In either case*

$$\min x(L) = G(\lambda) \quad \textit{where } \int_{G(\lambda)}^{\lambda} du/\beta(u) = 1. \tag{2}$$

## 3. The unimodal case

In order to see what the results should look like, we give a geometric description for the case when $\beta$ is unimodal. So we shall assume that

(iv) $\beta$ is increasing on $[0, x_0]$ and $\beta$ is decreasing on $(x_0, \infty)$. The extremals will depend on the relative size of $\lambda$ and $x_0 + \beta(x_0)$.

To motivate the results, we note that

$$x(L) = \lambda - \int_0^L g(s)\beta(x(s))\,ds \tag{3}$$

so that minimizing $x(L)$ is the same as maximizing the integral in (3). The strategy is to let $g = 0$ until $x(t_0) = x_0$ where $\beta$ is at its maximum. If $g(t) \equiv \varphi'(t)/\beta(x_0)$ on an interval $(t_0, t_1)$, then $x(t) \equiv x_0$ on this interval and $\beta(x(t))$ will be at its maximum value. Thus the control $\varphi$ is used to raise $x(t)$ to the value $x_0$ and then $g$ is used to try to stay at $x_0$.

Let $G(\lambda)$ be the minimum value. The results for the extremal controls are as follows. If $0 < \lambda \leqslant x_0$, then $\beta$ is increasing (this is the result of [1]),

$g = 0$ $\qquad$ $g$ satisfies $\int_b^L g(s)\,ds = 1$

$0$ $\qquad$ $\varphi(t) < \lambda$, $t < b$ $\qquad$ $\varphi(b) = \lambda$ $\qquad$ $\varphi(t) = \lambda \quad t \geqslant b$ $\qquad$ $L$

and

$$\int_{G(\lambda)}^{\lambda} \frac{du}{\beta(u)} = 1. \tag{4}$$

If $x_0 < \lambda < x_0 + \beta(x_0)$,

$g = 0$ $\qquad$ $g(s) = \dfrac{\varphi'(s)}{\beta(x_0)}$ $\qquad$ $g$ satisfies $\int_b^L g(s)\,ds = \dfrac{x_0 + \beta(x_0) - \lambda}{\beta(x_0)}$

$0$ $\qquad$ $\varphi(a) = x_0$ $\qquad$ $\varphi(b) = \lambda$ $\qquad$ $L$

$\varphi(t) < \lambda$, $t < b$ $\qquad$ $\varphi(t) = \lambda$, $t > b$

and

$$\int_{G(\lambda)}^{x_0} \frac{du}{\beta(u)} = 1 - \frac{(\lambda - x_0)}{\beta(x_0)}. \tag{5}$$

If $\lambda = x_0 + \beta(x_0)$,

$g = 0$ $\qquad$ $g(s) = \dfrac{\varphi'(s)}{\beta(x_0)}$ $\qquad$ $g = 0$

$0$ $\qquad$ $\varphi(a) = x_0$ $\qquad$ $\varphi(b) = \lambda$ $\qquad$ $L$

$\varphi(t) < \lambda$, $t < b$ $\qquad$ $\varphi(t) = \lambda$, $t > b$

and $G(\lambda) = x_0$.

If $\lambda > x_0 + \beta(x_0)$,

$g = 0$ $\quad g(s) = \dfrac{\varphi'(s)}{\beta(x_0)}$ $\quad g = 0$ $\quad g = 0$

$0$ $\quad \varphi(a) = x_0$ $\quad \varphi(b) = x_0 + \beta(x_0)$ $\quad \varphi(c) = \lambda$ $\quad L$

$\varphi(t) < \lambda$, $t < c$ $\quad \varphi(t) = \lambda$, $t > c$

and

$$G(\lambda) = \lambda - \beta(x_0). \tag{6}$$

The interpretation of the above diagram is that when $\varphi(t) = y$ is written, one means the leftmost $t$ which solves this equation. Note that in each case, the solution $x$ satisfies $x(a) = x_0$, and so by the definition of $g$ on $[a, b]$, $x(t) \equiv x_0$ on this interval. Note also that $G(\lambda)$ is a continuously differentiable function.

## 4. Analytic results

Our method of solving the optimal problem is to show that for each set of controls $\varphi$, $g$ and corresponding solution $x$ of (1), we can find one of a class of controls called special for which the corresponding solution $y$ satisfies $y(L) \leqslant x(L)$. Therefore the problem is reduced to minimizing over the special controls.

Definition. A set of controls $(\varphi, g)$ is called *special* if $\varphi$ and $g$ satisfy (ii) and (iii) and for some $x_0 \in (0, \lambda]$ and some numbers $a$ and $b$, $0 < a < b < L$; $\varphi(a) = x_0$; $g \equiv 0$ on $[0, a]$; $g(s) = \varphi'(s)/\beta(x_0)$ on $(a, b)$; and on $[b, L]$, either $g \equiv 0$ or $\varphi(t) \equiv \lambda$. The solution corresponding to special controls will be called a *special solution*.

Note that the controls of the previous section as well as those of Theorem 0 are special.

In order to simplify the notation of the propositions, suppose $x$ is a solution of (1), then define $\bar{x}$, by $\beta(\bar{x}) = \max_t \beta(x(t))$; and there is a $t$ such that $x(t) = \bar{x}$. There may be several $t$ that satisfy this for a given $\bar{x}$, and several $\bar{x}$ for a given solution $x(t)$. Any choice will do.

Proposition 1. *If $x(t)$ is a solution such that $\lambda \geqslant \bar{x} + \beta(\bar{x})$, then there is a special solution $y$ such that $y(L) \leqslant x(L)$.*

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PROOF. Since $x(L) = \lambda - \int_0^L g(s)\beta(x(s))\,ds \geqslant \lambda - \int_0^L g(s)\beta(\bar{x})\,ds = \lambda - \beta(\bar{x})$, we need only show that there is a special $y$ such that $y(L) = \lambda - \beta(\bar{x})$. To do this, fix $0 < a < b < L$ and let $\varphi$ satisfy (ii), $\varphi(a) = \bar{x}$, and $\varphi(b) = \bar{x} + \beta(\bar{x})$. Define $g$ by $g \equiv 0$ on $[0, a) \cup (b, L]$ and $g(s) = \varphi'(s)/\beta(\bar{x})$ on $[a, b]$. Then $\int_0^L g(s)\,ds = \int_a^b \varphi'(s)/\beta(x) = (\varphi(b) - \varphi(a))/\beta(\bar{x}) = 1$ and the corresponding solution $y$ of (1) satisfies $y(a) = \bar{x}$, $y'(t) \equiv 0$ on $[a, b]$, and $y'(t) = \varphi'(t)$ on $[b, L]$. It follows that $y(L) = \bar{x} + \int_b^L \varphi' = \bar{x} + \lambda - (\bar{x} + \beta(\bar{x})) = \lambda - \beta(\bar{x})$ as was to be shown.

The next two lemmas are in preparation for discussing the case when $\lambda < \bar{x} + \beta(\bar{x})$. The first says that is more efficient from the standpoint of the integral of $g$, to make a solution be $\bar{x}$ on an interval and then $\varphi$ a constant. The second says that without loss of generality, $\varphi$ rises to $\lambda$ before $t$ is $L$.

LEMMA 1. *Suppose $x$ is a solution of (1) corresponding to controls $(\varphi, g)$. Suppose that for some $r \leqslant s$, $x(r) = c \geqslant d = x(s) > 0$ and $x(t) \leqslant c$ on $[r, s]$. Assume further that $\beta(c) \geqslant \beta(x(t))$ on $[0, c]$. Define the controls $(\varphi_0, g_0)$ by $\varphi_0 \equiv \varphi$, $g_0 \equiv g$ on $[0, r]$, $\varphi_0(t) \equiv \varphi(s)$ on $[\frac{1}{2}(r + s), s]$ and $\varphi_0$ is an increasing differentiable function on $[r, \frac{1}{2}(r + s)]$ which satisfies the end conditions; $g_0 = \varphi_0'/\beta(c)$ on $[r, (r + s)/2]$ and $g_0(t) \equiv -2/(s - r)\int_c^d du/\beta(u)$ on $[\frac{1}{2}(r + s), s]$. Then $\int_r^s g_0(t)\,dt \leqslant \int_r^s g(t)\,dt$ and the solution $y$ on $[0, s]$ of (1) with controls $(\varphi_0, g_0)$ satisfies $y(s) = x(s)$.*

PROOF. Let $x$ be a solution satisfying the hypothesis of the lemma, and $(\varphi_0, g_0)$ the controls defined in the statement of the lemma. On $[r, s]$ we have

$$g = \varphi'/\beta(x) - x'/\beta(x)$$

and so

$$\int_r^s g(t)\,dt = \int_r^s \varphi'(t)\,dt/\beta(x(t)) - \int_c^d du/\beta(u). \tag{7}$$

Similarly

$$\int_r^s g_0(t)\,dt = \int_r^s \varphi_0'(t)\,dt/\beta(c) - \int_c^d du/\beta(u). \tag{8}$$

Note that $\int_r^s \varphi_0'(t)\,dt/\beta(c) = [\varphi_0(s) - \varphi_0(r)]/\beta(c) = [\varphi(s) - \varphi(r)]/\beta(c) = \int_r^s \varphi'(t)\,dt/\beta(c) \leqslant \int_r^s \varphi'(t)\,dt/\beta(x(t))$ since $\beta(c) \geqslant \beta(x(t))$. Combining (7) and (8) with this estimate gives

$$\int_r^s g_0(t)\,dt \leqslant \int_r^s g(t)\,dt.$$

Now the solution $y(t)$ satisfies $y(r) = x(r) = c$, $y(t) \equiv c$ on $[r, \frac{1}{2}(r + s)]$ and $y' = -g\beta(y)$ on $[(r + s)/2, s]$. Solving the differential equation one gets

$$\int_c^{y(s)} du/\beta(u) = \int_{\frac{1}{2}(r+s)}^s y'(t)\,dt/\beta(y(t)) = -\int_{\frac{1}{2}(r+s)}^s g_0(t)\,dt = \int_c^d du/\beta(u)$$

so that $y(s) = d = x(s)$.

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Lemma 2. *If $x$ is any solution of* (1) *with controls* $(\varphi, g)$ *then there are controls* $(\varphi_0, g_0)$ *such that* $\varphi_0(t_1) = \lambda$ *for some* $t_1 < L$ *and the corresponding solution* $y$ *satisfies* $y(L) = x(L)$.

Proof. In equation (1) replace $t$ by $2t$ and restrict $t$ to $[0, L/2]$. We have

$$x(2t) = \varphi(2t) - \int_0^{2t} g(s)\beta(x(s))\,ds = \varphi(2t) - \int_0^t 2g(2u)\beta(x(2u))\,du.$$

Now define $y(t) = x(2t)$, $\varphi_0(t) = \varphi(2t)$, $g_0(t) = 2g(2t)$ on $(0, L/2]$, and $y(t) \equiv x(L)$, $g_0 \equiv 0$, and $\varphi_0(t) \equiv \lambda$ on $[L/2, L]$. Then $y(t) = \varphi_0(t) - \int_0^t g_0(s)\beta(y(s))\,ds$ on $[0, L/2]$ and $y'(t) = 0 = \varphi_0'(t)$ on $[L/2, L]$. Thus $y$ is a solution to (1) and $\int_0^L g_0(t) = 1$ as is required.

Proposition 2. *Suppose $x$ is a solution of* (1) *such that* $\lambda < \bar{x} + \beta(\bar{x})$ *and* $x(L) \geqslant \bar{x}$. *Then there is a special solution $y$ with* $y(L) < x(L)$, *and* $y(t) \leqslant \bar{x}$ *on* $[0, L]$.

Proof. Let $\varphi$ and $g$ be the special controls defined by $0 < a < b < L$, $\varphi(a) = \bar{x}$, $\varphi(b) = \lambda$, $g \equiv 0$ on $[0,a]$, $g(s) = \varphi'(s)/\beta(\bar{x})$ on $(a, b)$ and $g \geqslant 0$ on $[b, L]$ such that $\int_0^L g = 1$. This last condition is possible since

$$\int_0^b g(t)\,dt = \int_a^b \varphi'(t)\,dt/\beta(\bar{x}) = (\lambda - \bar{x})/\beta(\bar{x}) < 1$$

by hypothesis. The corresponding solution $y$ satisfies $y(t) \equiv \bar{x}$ on $[a, b]$ and $y' = -g\beta(y)$ on $[b, L]$. Therefore

$$\int_{y(L)}^{\bar{x}} du/\beta(u) = \int_b^L g(t)\,dt = 1 - (\lambda - \bar{x})/\beta(\bar{x}) > 0, \tag{9}$$

so that

$$y(L) < \bar{x} \leqslant x(L).$$

For the next propositions, the reader is advised to draw some pictures. We will assume that $\varphi(t) = \lambda$ for some $t < L$.

Proposition 3. *Suppose $x$ is a solution of* (1) *such that* $\lambda < \bar{x} + \beta(\bar{x})$ *and* $x(L) \leqslant \bar{x} < \lambda$. *Suppose further that* $x(t) \nleqslant \bar{x}$ *for all $t$. Then there is a special solution $y$ such that* $y(L) \leqslant x(L)$. *Moreover* $y(t) \leqslant \bar{x}$ *on* $[0, L]$.

Proof. Let $x$ satisfy the hypothesis of the proposition and correspond to the controls $(\varphi, g)$. There is an $a \in (0, L)$ such that $\varphi(a) = \bar{x}$ and $b \in [a, L]$ such that $x(b) = \bar{x}$. (Note $x(t) \leqslant \varphi(t)$ on $[0, a]$). Finally, there is a $c \in (a, L)$ such that $\varphi(c) = \lambda$. Two cases arise depending on whether $c < b$ or not. Let us first consider the case when $b \leqslant c$. Define the controls $(\varphi_1, g_1)$ and $\varphi_1 \equiv \varphi$ on $[0, L]$; $g_1(t) = 0$ on $[0, a]$, $g_1 = \varphi_1'/\beta(\bar{x})$ on $(a, b)$, and $g_1 = g + h$ on $[b, L]$ where $h$ is a non-negative constant to be determined. It is clear that $g_1 \geqslant 0$, $y(t) = \varphi(t)$ on $[0, a]$, and $y(t) \equiv \bar{x}$ on $[a, b]$. Therefore,

$$\begin{aligned}
0 = y(b) - x(b) &= \int_0^b g(s)\beta(x(s))\,ds - \int_0^b g_1(s)\beta(y(s))\,ds \\
&= \int_0^b g(s)\beta(x(s))\,ds - \int_0^b g_1(s)\beta(\bar{x})\,ds \\
&\leqslant \int_0^b g(s)\beta(\bar{x})\,ds - \int_0^b g_1(s)\beta(\bar{x})\,ds \\
&= \beta(\bar{x})\left[\int_0^b g(s)\,ds - \int_0^b g_1(s)\,ds\right] \qquad (10)
\end{aligned}$$

so that $\int_0^b g(s)\,ds \geqslant \int_0^b g_1(s)\,ds$. Since

$$\begin{aligned}
1 = \int_0^L g_1(s)\,ds &= \int_0^b g_1(s)\,ds + \int_b^L g(s)\,ds + h(L-b) \\
&= \int_0^b g_1(s)\,ds + 1 - \int_0^b g(s)\,ds + h(L-b),
\end{aligned}$$

we have

$$h = \frac{1}{L-b}\left[\int_0^b g(s)\,ds - \int_0^b g_1(s)\,ds\right] \geqslant 0.$$

On $[b, L]$ $x' = \varphi' - g\beta(x)$ and $y' = \varphi' - g\beta(y) - h\beta(y)$ with $x(b) = y(b)$. If $h = 0$, $x \equiv y$, else by standard differential inequalities $y(t) \leqslant x(t)$ with $y(L) < x(L)$. Unfortunately, the controls $(\varphi_1, g_1)$ are not special. We apply Lemma 1, with $r = a$ and $s = L$ and $\varphi = \varphi_1$ to get $g_0 = 0$ on $[0, a]$, $\varphi_0'/\beta(\bar{x})$ on $[a, (a+L)/2]$, $\varphi_0 \equiv \lambda$ on $[(a+L)/2, L]$, and a solution $z$ of (1) with controls $(\varphi_0, g_0)$ such that $z(L) \leqslant y(L)$. The controls $(\varphi_0, g_0)$ are special except that $\int_0^L g_0(t)\,dt \leqslant \int_0^L g_1(t)\,dt = 1$. But again we can modify $g_0$ on $[(a+L)/2, L]$ by adding a constant to make $\int_0^L g_0(t)\,dt = 1$ and the resulting solution will lie below $z$, thus proving this case of the proposition.

The second case corresponds to $c < b$. Define the controls $(\varphi_0, g_0)$ by $\varphi_0 = \varphi$ on $[0, L]$; $g_0 = 0$ on $[0, a]$, $g_0 = \varphi_0'/\beta(\bar{x})$ on $[a, b]$. Again $y(b) = \bar{x} = x(b)$ so that (10) gives $\int_0^b g_0(s)\,ds \leqslant \int_0^b g(s)\,ds$. Then we may define $g_0 = g + h$, with $h$ a positive constant on $[b, L]$. As above, the resulting solution $y$ has $y(L) \leqslant x(L)$. This time $y$ is special.

**Proposition 4.** *Suppose $x$ is a solution such that $\lambda < \bar{x} + \beta(\bar{x})$ and $x(t) \leqslant \bar{x}$ on $[0, L]$. There exists a special solution $y$ such that $y(L) \leqslant x(L)$. Furthermore, $y(t) \leqslant \bar{x}$ for all $t$.*

PROOF. Let $x$ satisfy the hypothesis of the proposition. Let $\varphi(a) = \bar{x}$ and $x(b) = \bar{x}$. Since $x(t) \leqslant \varphi(t)$, we have $a \leqslant b$. Two cases arise. If $a = b$, then $x(t) = \varphi(t)$ on $[0, a]$ and $g \equiv 0$ there. We therefore may apply Lemma 1 with $r = a$ and $s = L$. We get controls $(\varphi_1, g_1)$ such that $g_1 \equiv 0$ on $[0, a]$, $g_1 = \varphi_1'(t)/\beta(\bar{x})$ on $[a, (a + L)/2]$, and $\varphi_1(t) \equiv \lambda$ on $[(a + L)/2, L]$. The corresponding solution $y$ satisfies $y(L) = x(L)$, but $\int_0^L g_0(t)\,dt \leqslant 1$. If $\int_0^L g_0(t)\,dt < 1$, modify $g_0$ on $[(a + L)/2, L]$ by adding an appropriate positive constant, finishing the proof as in the proof of the previous proposition.

If $a < b$, then define $\varphi_1 = \varphi$ on $[0, L]$ and $g_1 \equiv 0$ on $[0, a]$, with $g_1(t) = \varphi_1'(t)/\beta(\bar{x})$ on $[a, b]$. It follows that the solution $y$ with controls $(\varphi_1, g_1)$ satisfies $y(b) = \bar{x} = x(b)$. We then apply the computation (10) to get $\int_0^b g_1(t)\,dt \leqslant \int_0^b g(t)\,dt$. Again we define $g_1 = g + h$ on $[b, L]$ to make $\int_0^L g_1(t)\,dt = 1$. Then $y(L) \leqslant x(L)$. We now apply Lemma 1 with $r = b$, $s = L$ and $(\varphi, g)$ replaced by $(\varphi_0, g_0)$. These controls are special except possibly $\int_0^L g_0(t)\,dt < 1$. Again we add a constant to $g_0$ on $[(b + L)/2, L]$ to make $\int_0^L g_0(t)\,dt = 1$. The resulting solution $z$ will satisfy $z(L) \leqslant x(L)$. This completes the proof.

THEOREM 1. *Let $z(x)$ be defined by*

$$z(x) = \lambda - \beta(x) \quad \text{if } x + \beta(x) \leqslant \lambda \text{ and} \tag{11}$$

$$\int_{z(x)}^{x} du/\beta(u) = 1 - (\lambda - x)/\beta(x) \quad \text{if } x + \beta(x) > \lambda. \tag{12}$$

*Then $G(\lambda) = \inf\{x(L) | x$ is admissible$\} = \min_{0 \leqslant x \leqslant \lambda} z(x)$. Furthermore, a special solution is an extremal.*

PROOF. According to Propositions 1–4, $G(\lambda) = \inf\{x(L) | x \text{ is special}\}$. Consider first the case of a fixed $x \in [0, \lambda]$ (we have dropped the bar over the $x$). If $x + \beta(x) > \lambda$, and the special controls are of the form, $g \equiv 0$ on $[0, a] \cup [b, L]$ and $g(t) = \varphi'(t)/\beta(x)$ on $(a, b)$, then the associated solution $y$ satisfies $y(b) = x$, and $y' = \varphi'$ on $[b, L]$. Hence $y(L) \geqslant x$. On the other hand, if $g \equiv 0$ on $[0, a]$, $g(t) = \varphi'(t)/\beta(x)$ on $[a, b]$, and $\varphi(t) \equiv \lambda$ on $[b, L]$ then $y(L) \leqslant x$. Thus for a fixed $x$ and $\lambda < x + \beta(x)$, the best special satisfies $y' = -g\beta(y)$ on $[b, L]$ and therefore,

$$\int_x^{y(L)} du/\beta(u) = -\int_b^L g(t)\,dt = -\left[1 - \int_a^b g(t)\,dt\right]$$

so $\int_{y(L)}^x du/\beta(u) = 1 - [\beta(x)]^{-1}\int_a^b \varphi'(t)\,dt = 1 - (\lambda - \varphi(a))/\beta(x)$. But since $g \equiv 0$ on $[0, a]$, $\varphi(a) = x$, so $\int_{y(L)}^x du/\beta(u) = 1 - (\lambda - x)/\beta(x)$.

On the other hand, if for a fixed $x$, $x + \beta(x) \leqslant \lambda$ then Proposition 1 gives the minimum $y(L)$ as $\lambda - \beta(x)$. If $z(x)$ is defined as in the Theorem, then $G(\lambda) = \inf_{0 \leqslant x \leqslant \lambda} z(x)$. But note that if $\lambda = x + \beta(x)$ in (12) then $z(x) = x$, as it is in (11). Thus $z$ is continuous and the infimum is a minimum.

It is also useful to note that $z$ is differentiable whenever $\beta$ is, for implicit differentiation of (12) leads to

$$z'(x) = -\frac{\beta(z(x))}{\beta(x)^2}(\lambda - x)\beta'(x).$$

The critical points of $z$ are those of $\beta$. Noting that when $\lambda = x + \beta(x)$, $z(x) = x$ this formula agrees with differentiation of (11). Thus if $\beta$ is differentiable, so is $z$ and

$$z'(x)\beta'(x) \leqslant 0. \tag{13}$$

THEOREM 2. *If $\beta$ is unimodal then the results of Section 3 are correct.*

PROOF. In this case the only critical point of $z$ is $x_0$ and $z$ has a minimum there according to (13), and $z(x_0) = G(\lambda)$.

## 5. The physical interpretations

In order to give some ideas on the physical meaning of the above results, we note that in the two-step enzymatic reaction, points of increase of $\varphi$ are the points of positive density of the first enzyme. The function $g$ is the density function of the second enzyme. The number $\lambda$ is the amount of the precursor absorbed in the liver. If $\beta$ is monotone increasing on $[0, \lambda]$ then Theorem 0 applies. The optimal control therefore obtains when all of the density of the first enzyme precedes that of the second. However, if $\lambda$ exceeds the maximum of $\beta$, for example when $\beta$ is unimodal, then the support of the densities overlap. In the case when $\lambda$ is sufficiently large, i.e. $\lambda > x_0 + \beta(x_0)$ (see (6)), some of the first enzyme is located downstream of all the second enzyme. This suggests that the liver should operate with the goal of keeping $\lambda$ small. This would mean that the first enzymatic reaction should be slow.

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