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OPTIMAL NUTRITIONAL INTAKE FOR FETAL GROWTH

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Abstract. The regular nutritional intake of an expectant mother clearly affects the weight development of the fetus. Assuming the growth of the fetus follows a deterministic growth law, like a logistic equation, albeit dependent on the nutritional intake, the ideal solution is usually determined by the birth-weight being pre-assigned, for example, as a percentage of the mother's average weight. This problem can then be specified as an optimal control problem with the daily intake as the control, which appears in a Michaelis-Menten relationship, for which there are well-developed procedures to follow. The best solution is determined by requiring minimum total intake under which the preassigned birth weight is reached. The algorithm has been generalized to the case where the fetal weight depends in a detailed way on the cumulative intake, suitably discounted according to the history. The optimality system is derived and then solved numerically using an iterative method for the specific v alues of parameter. The procedure is generic and can be adapted to any growth law and any parameterisation obtained by the detailed physiology.

1. **Introduction.**

Pregnancy is an important event in the life of a female mammal, needed for reproduction of its progeny and maintaining the integrity of the species. Following fertilization, the embryo implants in the uterine cavity of the female mammal and develops into a fetus. It receives nutrition from the mother through the placenta and umbilical cord. Then, the fetus will develop further until the time of birth. The conceptus, the product of fertilization such as the fetus, placenta,

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etc., will develop intrauterine in three stages. The first stage called cleavage is the process of cell division without growth or differentiation from zygote. The second stage, differentiation, is the process of forming specific organs. The third stage, fetal growth, occurs once the differentiation stage has been completed.

It has been suggested that growth and development of the fetus are influenced by the maternal nutrient intake which affects the size and weight of the fetus (Redmer et al., 2004 [8]). Animal studies show that both maternal undernutrition and overnutrition during pregnancy reduce placental-fetal blood flows and stunt fetal growth (Wu et al., 2004 [9]). Wu et al. (2006) [10] suggested that the fetal growth is influenced by complex interactions between genetic, epigenetic and environmental factors and that the placental and fetal growth is vulnerable to maternal undernutrition or overnutrition throughout gestation. This suggests that the history of nutrient intake plays an important role in fetal growth.

In this paper, we consider the fetal growth in a singleton pregnancy of a specific mammal such as sheep in the second half of pregnancy after the differentiated fetus is formed. We use the birth weight as an indicator of the health of both the fetus and the mother assuming that if the birth weight is greater than a set value (for example, a certain percentage of the mother's average weight), an injury could be caused to both the mother and the fetus during labour, while if the birth weight is less than the set value, the mortality and morbidity rate of the newborn will increase. Our goal is to find the daily nutrient intake that will achieve a desirable birth-weight while minimizing the total nutrient intake in the second half of the pregnancy. Such strategy could potentially increase the quality of post-natal life-history, and, in the case of farmed mammals, give a better economic output.

Optimal control strategies have been used before to study biological systems. For example, the optimal treatment of various infectious diseases such as HIV and TB was calculated in the papers (Joshi, 2002 [2]; Jung et al., 2002 [3]; Kirschner et al., 1997 [5]; Zaman et al., 2007 [11]). Optimal control theory was also used in the harvesting, glucose uptake and predator-prey models (Lenhart et al., 2007 [6]) where some objective functional was minimized. We implement this body of knowledge in control theory in our problem, where the end point is set, and we show under what conditions the optimal nutrient intake is constant.

First, we justify the use of the logistic equation as a model for fetal growth. We then describe the optimal control problem and show some numerical results.

2. Optimal control problem.

Our goal is to find the daily nutrient intake that will achieve a desirable birth-weight while minimizing the total nutrient intake in the second half of the pregnancy. We therefore wish to minimize $J\{u\} = \int_{t_0}^{t_b} u\, dt$, where u is the daily nutrient intake, subject to an ordinary differential equation $\dot{x} = f(x,u)$ that describes fetal growth where x is the fetal weight as a function of time t, with growth function f.

2.1. Modeling of fetal growth.

Our model of fetal growth is based on experimental data of sheep singleton pregnancies in Australia during the second half of the pregnancy (Gatford et al.,2008 [4]). Experimental data is not available for the first half of the pregnancy when the fetus is very small. Hence the data in Table 1 is for the second half of the pregnancy (about 72 days) only. Figure 1 shows the experimental data (marked with *) and the best fit of several functions. The solid line describes the logistic equation, $\dot{x}(t) = rx\left(1 - \frac{x}{K}\right)$ which implies $x\left(t\right) = \frac{x_0 K}{x_0 + (K - x_0)e^{-rt}}$. The dashed line describes the straight line function, $x(t) = x_0 + rt$. The dash-dot line describes the Gompertz function, $x(t) = x_0 e^{\left\{\ln\left(\frac{K}{x_0}\right)\left(1-e^{-rt}\right)\right\}}$. The dotted line describes the exponential function, $x(t) = x_0 e^{rt}$. As shown in Figure 1 the logistic equation gives the best fit for data with the coefficient of determination $R^2 = 0.983$. The Gompertz, exponential and straight line functions give R^2 of 0.98, 0.59 and 0.892, respectively ($R^2 = 1$ indicates a perfect fit).

Time since conception (days)	Fetal weight (kgms)
75	0.202
84	0.360
101	0.844
109	1.434
116	2.128
121	2.825
122	2.675
132	4.200
133	4.083
145	5.433
147	4.900
Birth	

TABLE 1. Experimental data from sheep, from Gatford et al., 2008 [4].

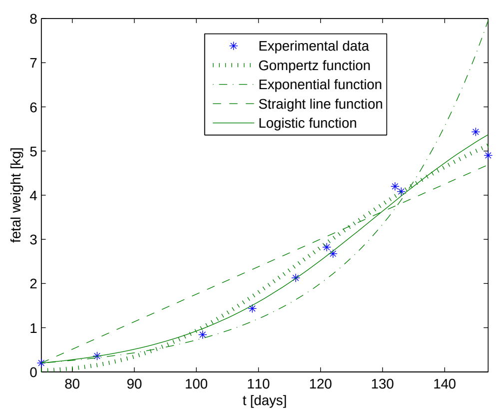

FIGURE 1. the sheep fetal weight in kg from day 75 to day 147 (the second half of the pregnancy) in various functional forms for growth, plotted together with the experimental data.

To include the nutritional intake as a control in the logistic equation, we multiply r by the Michaelis-Menten relationship $\frac{u}{u+L}$. This ensures that when there is no nutrient intake ($u = 0$) there is no growth, while for high intake ($u >> L$) Michaelis-Menten relationship is 1 and the growth function behaves like the logistic equation. For low intake $0 < u << L$, we get a linear response with u.

Firstly, we consider the carrying capacity (K) as a constant $K = 7$ kg. This is of course a "mythical limit to growth" as birth occurs at a weight level before K occurs. Secondly, after modifying the model to make it more realistic (taking into account the fact that the history of nutrient intake plays an important role in fetal growth), the carrying capacity (K) is represented as a prescribed function of the cumulative intake using empirical relationships suggested by data analysis. Here the carrying capacity $K > 0$ is presumed to depend on y according to $K = K_0 + \frac{ay}{y+L_0}$ where $y(t) = \int_0^t e^{-\beta(t-s)} u(s)\, ds$ is a function of a cumulative intake (suitably discounted according to the history), $\beta > 0$ is the discount factor which indicates the extent to which the cumulative intake is influenced by the past, $a > 0$ is the factor which indicates the degree to which the ultimate weight is de termined by the input and K_0 and L_0 are positive constants.

In the case of sheep fetal growth, with 72 days for the second half of the pregnancy, our optimal control problem then becomes:

minimize $\qquad J\{u\} = \int_0^{72} u\, dt$

subject to the ordinary differential equations:

$$\frac{dx}{dt} = \frac{rux}{u+L}\left(1 - \frac{x}{K_0 + \frac{ay}{y+L_0}}\right)$$
$$\frac{dy}{dt} = u - \beta y$$

with boundary conditions: $x(0) = 0.2, x(72) = 5.5$ and $y(0) = 0$, where $x(t)$ is the fetal weight in kg at time $t, u(t)$ is the daily nutrient intake in kg $\cdot$ days^{-1} at time $t, r > 0$ is the specific growth rate and L is a positive constant.

2.2. **Solution of the optimal control problem.** Solving the optimal control problem using Pontryagin's Maximum Principle (See Appendix in which it is explicitly given for general growth functions) leads to the following system of ordinary differential equations:

$$\dot{x} = \frac{rux}{u+L}\left(1 - \frac{x}{K_0 + \frac{ay}{y+L_0}}\right) \tag{1}$$
$$\dot{y} = u - \beta y \tag{2}$$
$$\dot{u} = \frac{-(u+L)\left\{\begin{array}{l} axL_0(\lambda_2+1)\left(\alpha y L + u^2\right) \\ +\lambda_2 \alpha L(K_0 y + K_0 L_0 + ay) \\ (K_0 y + K_0 L_0 + ay - xy - xL_0) \end{array}\right\}}{2(\lambda_2+1)(y+L_0)(K_0 y + K_0 L_0 + ay)} \tag{3}$$
$$\dot{\lambda}_2 = \frac{aL_0 ux(\lambda_2+1)(u+L)}{L(K_0 y + K_0 L_0 + ay)(K_0 y + K_0 L_0 + ay - xy - xL_0)} \tag{4}$$

with the boundary conditions: $x(0) = 0.2, x(72) = 5.5, y(0) = 0$ and $\lambda_2(72) = 0$.

In the special case $a = 0$, the carrying capacity K is a constant and

$$\frac{dx}{dt} = \frac{rux}{u+L}\left(1 - \frac{x}{K}\right) = f_1(x) \cdot f_2(u).$$

In this case $u =$ constant as can be seen from the following theorem.

Theorem 2.1. *If $\dot{x} = f(t, x, u) = f_1(x) \cdot f_2(u)$ is separable and g is not a function of x, $g = g(t, u)$ where g comes from $J\{u\} = \int_{t_0}^{t_b} g[t, u(t)]\, dt$ then $\dot{u} = G(t, x, u) \equiv 0$, and so u is a constant.*

Proof. Assume that $\dot{x} = f(t, x, u) = f_1(x) f_2(u)$.
It has been shown in the Appendix that $\dot{u} = \frac{g_x f_u^2 - g_{ux} f f_u - g_u f_x f_u + g_u f_{ux} f}{g_{uu} f_u - g_u f_{uu}}$.
Since $g = g(t, u)$, then $g_x = g_{ux} = 0$, so

$$\dot{u} = \frac{-g_u f_1'(x) f_2(u) f_1(x) f_2'(u) + g_u f_1'(x) f_2'(u) f_1(x) f_2(u)}{g_{uu} f_1(x) f_2'(u) - g_u f_1(x) f_2''(u)} = 0.$$

Here f' is the derivative with respect to the nominated function variable. Hence, $\dot{u} = 0$ which means that u is a constant. □

Note that by substituting $a = 0$ in equation(4) one gets $\dot{\lambda}_2 = 0$ and therefore λ_2 = constant = 0 (due to the boundary condition). By substituting $a = 0$ and $\lambda_2 = 0$ into equation(3),the numerator in equation (3) becomes zero and one gets the same result.

3. **Numerical results.**

In this section, we show a specific example of optimal nutrient intake that achieves a desired fetal weight. The optimal control problem described by equations(1)-(4) was solved by the bvp4c command in MATLAB (this is a finite difference code that implements the three-stage Lobatto IIIA formula).

Figure 2 shows the sheep fetal weight in kg over the 72 days of the second half of the pregnancy, plotted together with the experimental data, with the following parameters and boundary conditions: $t_0 = 0$ days, $t_b = 72$ days, $x(0) = 0.2$ kg, $x(72) = 5.5$ kg, $y(0) = 0$, $r = 0.07$ days^{-1}, $L = 0.09$ kg $\cdot$ days^{-1}, $a = 0.1$ kg, $L_0 = 10$ kg, $\beta = 0.12$ days^{-1} and $K_0 = 7$ kg. Note that this is a solution of the optimal control. We did not attempt to fit parameters to the experimental data here (but used the same K_0 and r used in Figure 1). Nevertheless, as seen in Figure 2, the calculated fetal weight still fits the data very well. There is a slight improvement of R^2, ($R^2 = 0.985$) compared to Figure 1 which suggests that the modified model with the carrying capacity K a function of the cumulative intake, is more appropriate with respect to the experimental data than the old one with K a constant.

Figure 3 illustrates the true minimum daily nutrient intake in kg per day over the same period to achieve the pre-set birth-weight. This graph shows that the food intake is increasing in the first and middle third of the second half of pregnancy and largest in the last third of the second half of pregnancy. Note that although the daily nutrient is decreasing fast before birth, the animal is still feeding at the birth-time and the value of the food intake is not, of course, going to zero. The variation in the food intake is not very large, but this depends on the model parameters.

The total nutrient intake is calculated by $\int_0^{72} u dt = 127.1$ kg.

For the case $a = 0$, where $K = 7$ is a constant, we obtain that u is a constant equals 2.0 kg.days^{-1} and the total intake for the mother in the second half of the pregnancy is $\int_0^{72} u dt = 145.9$ kg.

4. **Discussion and conclusion.**

In this paper we have developed a generic approach for calculating the daily nutrient intake that achieves a desirable birth-weight while minimizing the total nutrient intake. The algorithm we derived allows for a

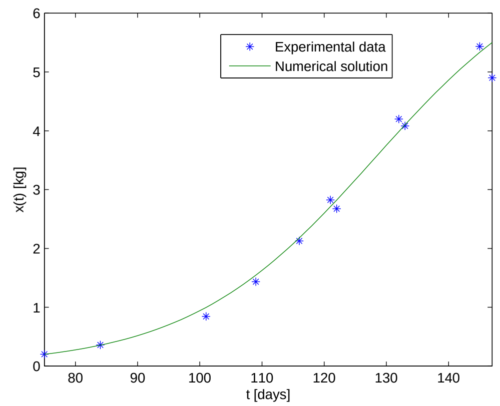

FIGURE 2. the sheep fetal weight in kg over the 72 days of the second half of the pregnancy, plotted together with the experimental data.

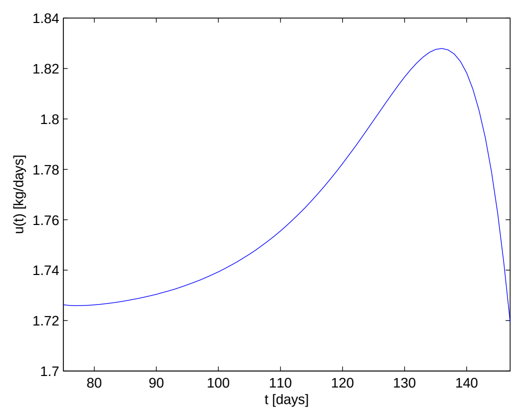

FIGURE 3. The true minimum daily nutrient intake in kg per day over the same period as in Figure 2 to achieve the pre-set birthweight.

direct calculation of the control variable u, which now appears explicitly as a component function in the dynamical system, without calculating all the solutions of the adjoint equation(s).

This allowed us to prove that in the case of constant carrying capacity where the equation for the control is separable in terms of the state and control variables and the objective functional depends only on the control, the optimal nutrient intake is a constant.

We applied the algorithm to the more generalized case where the fetal weight depends on the cumulative intake, suitably discounted according to the history. The procedure could also be applied to other functions of fetal growth.

Finding the optimal nutrient intake that achieves a desirable birth-weight increases the quality of post-natal life-history, and, in the case of farmed mammals, gives a better economic output.

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Appendix.

One-dimensional optimal control problem. Suppose we want to

maximize (or minimize)

$$J\{u\} = \int_{t_0}^{t_b} g\left[t, x\left(t\right), u\left(t\right)\right] dt$$

subject to

$$\frac{d}{dt}x\left(t\right) = f\left(t, x\left(t\right), u\left(t\right)\right), \qquad x(t_0) = x_0 \quad \text{and} \quad x(t_b) = x_b. \tag{5}$$

where $u(t)$ and $x(t)$ are the control and state variables, respectively.

The principle technique for such an optimal control problem is to solve a set of necessary conditions that an optimal control and corresponding state must satisfy (Clark, 1976 [1]).

The Pontryagin's Maximum Principle (Pontryagin et al., 1962 [7]) gives a Hamiltonian expression, H, which is defined as follows:

$$H\left(t, x, u, \lambda\right) = g\left(t, x, u\right) + \lambda f\left(t, x, u\right).$$

It has been shown (see for example, Lenhart et al., 2007 [6]) that by maximizing (or minimizing) H we also maximize (or minimize) the objective functional, J. Assuming that a piecewise continuous optimal control exists and let $u^*(t)$ be an optimal control and $x^*(t)$ be an optimal corresponding state, the necessary conditions can be written in terms of the Hamiltonian:

$$\frac{\partial H}{\partial u} = 0 \text{ at } u^* \;\Rightarrow\; g_u + \lambda f_u = 0, \quad \text{(optimality condition)},$$

$$\dot{\lambda} = -\frac{\partial H}{\partial x} \quad => \dot{\lambda} = -\left(g_x + \lambda f_x\right), \quad \text{(adjoint equation)},$$

$$\dot{x} = f\left(t, x, u\right) = \frac{\partial H}{\partial \lambda}, \quad x\left(t_0\right) = x_0, x\left(t_b\right) = x_b, \quad \text{(state equation)}.$$

After generating the state and the adjoint equation, we then obtain the dynamical system:

$$\dot{x} = f\left(t, x\left(t\right), u\left(t\right)\right) \tag{6}$$
$$\dot{\lambda} = p\left(t, x\left(t\right), u\left(t\right), \lambda\left(t\right)\right) \tag{7}$$

with the boundary conditions: $x\left(t_0\right) = x_0$ and $x\left(t_b\right) = x_b$.

Next, we will solve the above system for $x^*(t)$ and $\lambda(t)$. By solving the optimality condition, $\frac{\partial H}{\partial u} = 0$, we obtain the required function of $u^*(t)$, then substituting $x^*(t)$ and $\lambda(t)$ we obtain $u^*(t)$.

We represent the general formulae of $\dot{u}$ suitable for the optimal control problem which has only one state equation, $\dot{x} = f(t, x(t), u(t))$.

From the optimality condition, $H_u = g_u + \lambda f_u = 0$, we differentiate H_u with respect to t and use the chain rule:

$$\frac{\partial g_u}{\partial x}\dot{x} + \frac{\partial g_u}{\partial \lambda}\dot{\lambda} + \frac{\partial g_u}{\partial u}\dot{u} + \dot{\lambda} f_u + \lambda\left(\frac{\partial f_u}{\partial x}\dot{x} + \frac{\partial f_u}{\partial \lambda}\dot{\lambda} + \frac{\partial f_u}{\partial u}\dot{u}\right) = 0.$$

Since $\frac{\partial g_u}{\partial \lambda} = 0$ and $\frac{\partial f_u}{\partial \lambda} = 0$, we obtain

$$\frac{\partial g_u}{\partial x}\dot{x} + \frac{\partial g_u}{\partial u}\dot{u} + \dot{\lambda} f_u + \lambda\frac{\partial f_u}{\partial x}\dot{x} + \lambda\frac{\partial f_u}{\partial u}\dot{u} = 0.$$

Substituting $\dot{\lambda} = -(g_x + \lambda f_x)$ and $\dot{x} = f(t, x, u)$, we get

$$\begin{aligned} g_{ux} f + g_{uu}\dot{u} + (-g_x - \lambda f_x) f_u + \lambda f_{ux} f + \lambda f_{uu}\dot{u} &= 0 \\ (g_{uu} + \lambda f_{uu})\dot{u} &= -g_{ux} f + g_x f_u + \lambda f_x f_u - \lambda f_{ux} f \\ \dot{u} &= \frac{-g_{ux} f + g_x f_u + \lambda f_x f_u - \lambda f_{ux} f}{g_{uu} + \lambda f_{uu}} \quad . \end{aligned}$$

Since $g_u + \lambda f_u = 0,$ we have $\quad \lambda = \frac{-g_u}{f_u}$, so that

$$\dot{u} = \frac{g_x f_u^2 - g_{ux} f f_u - g_u f_x f_u + g_u f_{ux} f}{g_{uu} f_u - g_u f_{uu}}. \tag{8}$$

We have thus simplified the original algorithm by formulating the alternative system including an equation for $\dot{u}(t)$ with $\dot{\lambda}(t)$ and $\lambda(t)$ eliminated from the system.

Two-dimensional optimal control problem. For the optimal control problem in this paper, we generate two state equations as in equations(1)-(2) so that the Pontryagin's Maximum Principle (Pontryagin et al., 1962 [7]) gives a Hamiltonian, H, which enables us to determine the control u as a piecewise continuous control function $u : [t_0, t_b] \to [0, \infty)$, as follows:

$$H = u + \lambda_1 \frac{rux}{u + L}\left(1 - \frac{x}{K_0 + \frac{ay}{y + L_0}}\right) + \lambda_2 (u - \beta y).$$

with the adjoint equations:

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial x} \quad = \frac{-\lambda_1 ru}{u + L}\left(1 - \frac{2x}{K_0 + \frac{ay}{y + L_0}}\right) \tag{9}$$

and

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial y} \quad = \frac{-\lambda_1 a r L_0 u x^2}{\left(K_0 + \frac{ay}{y + L_0}\right)^2 (u + L)(y + L_0)^2} \quad + \quad \beta\lambda_2 \tag{10}$$

for which $\lambda_2(t_b) = 0$. This last boundary condition follows from the fact that we have no value for y at $t = t_b$.

By considering the optimality condition, $\frac{\partial H}{\partial u} = 0$ and solving for u^*, subject to the constraints, the characterizations of u^* can be derived. To illustrate the characterizations of u^*, we have

$$\frac{\partial H}{\partial u} = 1 + \lambda_1 \frac{rLx}{(u+L)^2}\left(1 - \frac{x}{K_0 + \frac{ay}{y+L_0}}\right) + \lambda_2 = 0. \tag{11}$$

This formally determines the control as the function

$$u^*(t) = \sqrt{-\frac{\lambda_1 rLx}{(1+\lambda_2)}\left(1 - \frac{x}{K_0 + \frac{ay}{y+L_0}}\right)} - L. \tag{12}$$

Furthermore, we obtain the second derivative

$$\frac{\partial^2 H}{\partial u^2} = -\lambda_1 \frac{2rLx}{(u+L)^3}\left(1 - \frac{x}{K_0 + \frac{ay}{y+L_0}}\right). \tag{13}$$

Hence, the strict Legendre condition $\frac{\partial^2 H}{\partial u^2} > 0$ is satisfied on $[t_0, t_b]$, if $\lambda_1(t) < 0$ for $t \in [t_0, t_b]$ holds and since in our case $x, u > 0$ and $x < K_0 + \frac{ay}{y+L_0}$.

Following the usual procedure for solving optimal control problems, we obtain the system in the form of $\dot{\lambda}_1 = -\frac{\partial H}{\partial x}$, $\dot{\lambda}_2 = -\frac{\partial H}{\partial y}$, $\dot{x} = f_1(t, x, y, u)$ and $\dot{y} = f_2(t, x, y, u)$ which can be solved to obtain $\lambda_1(t), \lambda_2(t), x(t)$ and $y(t)$ which could then be substituted into Eq. (12) to obtain the optimal control u.

By differentiating $\frac{\partial H}{\partial u}$ with respect to time, the above algorithm could be simplified in a similar way to the one described in the previous section by formulating the alternative system including an equation for $\dot{u}$ as shown for the system in Section 2.2, equation(3), where $\dot{\lambda}_1(t)$ and $\lambda_1(t)$ are eliminated from the system. This is achieved since equation (10) determines λ_1 and then we obtain $\dot{\lambda}_1$ from equation (9). Thus we obtain the alternative system in equations (1)–(4), in which the control function appears explicitly.

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