Documento Suplementar 2

Fisiologia Matemática, biologia matemática, e biomatemática: leptina e a busca pelo controle de peso

Fisiología Matemáticas, biología matemática y biomatemáticas: la leptina y la búsqueda de control de peso

Mathematical physiology, mathematical biology, and biomathematics: leptin and the weight control mechanisms

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Resumo

Neste material se discuti o modelo matemático e código do artigo principal. Usa-se Matlab para gerar as simulações. A modelagem é baseado no conceito de Controle Integral-Proporcional (PI) e sistemas dinâmicos. Somente leptina é usada para simular variações de peso como resultado de condições diversas como resistência à leptina e mudança de dieta. Apesar de que várias simulações são feitas, somente alguns casos considerados interessantes são reportados. Adicionalmente, uma analise de sensibilidade dos parâmetros é feita como forma de estudar o modelo.

Descritores: Homeostase, Leptina, Matemática, Simulação por Computador , Peso Corporal.

Resumen.

En este artículo se discute el modelo matemático y el código del artículo principal. Hacemos uso de Matlab para generar las simulaciones. El modelado se basa en el concepto de Control-Proporcional Integral (PI) y sistemas dinámicos. Sólo leptina se utiliza para simular los cambios de peso como resultado de varias condiciones tales como resistencia a la leptina y el cambio de dieta. A pesar de se hacen varias simulaciones, sólo unos pocos casos considerados interesantes son reportados. Además, un análisis de sensibilidad de parámetros se realiza con el fin de estudiar el modelo.

Descriptores. Homeostasis, Leptina, Matemáticas, Simulación por Computadora, Peso Corporal.

Abstract

On this article we discuss the mathematical model and codes used on the main article. We make use of Matlab for running the simulations. The modelling relies on Proportional-Integral Control (PI) and dynamical systems. Just leptin is used for

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simulating variations of body weight under several conditions such as leptin resistance and diet changes. Notwithstanding several simulations were carried out, just some cases is reported considered interest. Further, an analysis of sensitivity is done on some parameters of the model expecting to have a better idea of the model behaviour.

Key words. Homeostasis, leptin, mathematics, Computer Simulations, Body weight.

1. Introdução

Neste material se apresenta um conjunto de códigos complementares aos apresentados na primeira parte deste material. No primeiro código, Simulink deve ser usado, neste código, somente Matlab® é necessário. Usa-se a função ODE42, disponível em Matlab como biblioteca padrão para resolver equações diferenciais; geralmente bastante documentação pode ser achada na internet.

2. Códigos

2.1 Parametrização

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%                  GNU GENERAL PUBLIC LICENSE
%                   Version 3, 29 June 2007
%           https://www.gnu.org/copyleft/gpl.html
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

% Model parameters

global k1 k2 k3 k4 k5 k6 k7 k8
global FFM  SetPt beta alfa R_syn GFR RenClearance pho_fat pho_food
global a1 a2 a3 a4 c1 c2

k1=1.42;%ng/g
k2=15.6;%ng/ml
k3=0.00272;%ml/g
k4=5.6;%g/day
k5=0.55;%ng/g
k6=0.24432;%kcal/g/day
k7=1;%N/A
k8=0.22;%ng/g
FFM=22;%g
beta=1.5;
alfa=0.022;

R_syn=51.84;%ng/g/day
GFR=284.4;%ml/day
RenClearance=0.25;%N/A
pho_fat=9; %kcal/g
pho_food=3.2;%kcal/g

a1=-0.24;%g^2/ng/day
a2=-288;%g^2/ng/day^2
```

```
a3=80.2469; %cal/ng/day
a4=243.4089; %kcal/ng/day^2
SetPt=0.3370;
c1=3.4724;
c2=11.1116;

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%
% Main References
%
% Tam, J.; Fukumura, D.;  Jain, R. K.; A mathematical model of murine
% metabolic regulation by leptin: energy balance and defense of a
stable
% body weight. Cell Metab. 2009 January 7; 9(1): 52-63.
% doi:10.1016/j.cmet.2008.11.005.
%
% Uluseker, C.; Mathematical Model for
% Leptin Dynamics. Master of Science Thesis, MathMods Erasmus Mundus
M.Sc.
% Programme, Mathematical Models in Life and Social Sciences.
Department of
% Information Engineering, Computer Science and Mathematics.
University of
% L'Aquila: Italy: 2014.
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

2.2 Modelo (*equações*)

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%                  GNU GENERAL PUBLIC LICENSE
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%           https://www.gnu.org/copyleft/gpl.html
%           Author: Costanzo Manes, 2015
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function xdot=leptin_model(t,x)

% Leptin Model from paper:
% "A mathematical model of murine metabolic regulation by leptin..."
% By J. Tam, D. Fukumura, R.K. jain, Cell Metab. 2009

xdot=0*x;

global k1 k2 k3 k4 k5 k6 k7 k8
global FFM  SetPt beta alfa R_syn GFR RenClearance pho_fat pho_food
global a1 a2 a3 a4 c1 c2

global SetPmodel Settling
% Set point model:      SetPmodel=1; Settling=0;
% Settling point model: Settling=1; SetPmodel=0;

% State variables
Lep_plasma=x(1); % Leptin in plasma
E=x(2);          % Stored Energy
```

```
if SetPmodel
    IntErr=x(3);     % Integral of the error
end

% Fat Mass
FM=E/pho_fat;
% Body Mass
BM=FM+FFM; % [Equation 7]
% Blood Volume
BV=alfa*BM+beta;

Lep_brain=k1*Lep_plasma/(k2+Lep_plasma)+k3*Lep_plasma; % [Eq. 2]

% Set point model: Proportional + Integral term
if SetPmodel
   FoodIntake=a1*(Lep_brain - SetPt)+a2*IntErr + c1;    % [Equation 8]
   Eout=BM*(a3*(Lep_brain - SetPt)+a4*IntErr+c2);       % [Equation 9]
end

% Settling point model
if Settling
   FoodIntake=k4*(1-Lep_brain/(k5+Lep_brain));         % [Equation 3]
   Eout=k6*BM*(1+k7*Lep_brain/(k8+Lep_brain));         % [Equation 5]
end

Ein=pho_food*FoodIntake;    % [Equation 4]

xdot(1)=(FM*R_syn-GFR*RenClearance*Lep_plasma)/BV;      % [Equation 1]
xdot(2)=Ein-Eout;               % [Equation 6]

if SetPmodel
   xdot(3)=Lep_brain - SetPt;  % Integral of the error
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%
% Main References
%
% Tam, J.; Fukumura, D.;  Jain, R. K.; A mathematical model of murine
% metabolic regulation by leptin: energy balance and defense of a
stable
% body weight. Cell Metab. 2009 January 7; 9(1): 52-63.
% doi:10.1016/j.cmet.2008.11.005.
%
% Uluseker, C.; Mathematical Model for
% Leptin Dynamics. Master of Science Thesis, MathMods Erasmus Mundus
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% Programme, Mathematical Models in Life and Social Sciences.
Department of
% Information Engineering, Computer Science and Mathematics.
University of
% L'Aquila: Italy: 2014.
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

2.3 principal (*coordenador*)

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%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
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%           https://www.gnu.org/copyleft/gpl.html
%           Author: Costanzo Manes, 2015
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

% leptin_main
% main program that simulates the Leptin model in
% "A mathematical model of murine metabolic regulation by leptin..."
% By J. Tam, D. Fukumura, R.K. jain, Cell Metab. 2009

% needs:
%   Model parameters.m
%   leptin_model.m

close all, clear all, clc

% Define Simulation Interval
dt=0.1;  Tend=30;
Tsim=0:dt:Tend;

% Set model type
global SetPmodel Settling
%SetPmodel=1;  Settling=1-SetPmodel;
 Settling=0;   SetPmodel=1-Settling;
% Note:
%    Set point model:      SetPmodel=1; Settling=0;
%    Settling point model: Settling=1; SetPmodel=0;


% setting parameters
mod_parameters

% a2=a2/10;
% a4=a4/10;

% Initial values
% E_0 FM_0 Lep_plasma_0

FM_0=2;  %g
E_0=FM_0*pho_fat;  %g*kcal/g=kcal
Lep_plasma_0=(FM_0*R_syn)/(GFR*RenClearance); %
(g*(ml/week)/((ml/week)*(N/A)))=g;

% Initial state
if SetPmodel
   x0=[ Lep_plasma_0; E_0; 0];
end
if Settling
   x0=[ Lep_plasma_0; E_0];
end

[T,X]=ode45('leptin_model',Tsim,x0);

Lep_plasma=X(:,1);
Fat_mass=X(:,2)/pho_fat;

if SetPmodel
```

```
    Titolofig='Set Point Simulation';
end
if Settling
    Titolofig='Settling Point Simulation';
end

figure(1)
title(Titolofig)
subplot(211)
plot(T,Lep_plasma), grid
ylabel('Plasma Leptin')
subplot(212)
plot(T,Fat_mass), grid
ylabel('Fat mass')
set(1,'Position',[10 20 830 560])
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%
% Main References
%
% Tam, J.; Fukumura, D.;  Jain, R. K.; A mathematical model of murine
% metabolic regulation by leptin: energy balance and defense of a
stable
% body weight. Cell Metab. 2009 January 7; 9(1): 52-63.
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% Leptin Dynamics. Master of Science Thesis, MathMods Erasmus Mundus
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Department of
% Information Engineering, Computer Science and Mathematics.
University of
% L'Aquila: Italy: 2014.
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
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3. Considerações finais

Para usar o código, somente se precisa criar os arquivos para cada pedaço de código, colocá-los na mesma localização no computar e chamar o código na seção 2.3.

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