PERIODICA POLYTECHNICA SER. EL. ENG. VOL. 50, NO. 1–2, PP. 23–32 (2006)

EXTENSION OF THE BERGMAN MINIMAL MODEL FOR THE GLUCOSE-INSULIN INTERACTION

Levente KOVÁCS

Department of Control Engineering and Information Technology
Budapest University of Technology and Economics
H–1117 Budapest, Magyar Tudósok krt. 2, Hungary
e-mail: lkovacs@seeger.iit.bme.hu

Received: April 28, 2005

Abstract

In this paper, the extension of the Bergman model (minimal model) is proposed with an internal insulin control (IIC) part, representing the own insulin control of the human body. The model has been verified with clinical experiments, by oral glucose intake tests. Employing parameter estimation, for inverse problem solution technique (SOSI – 'single output single input') was developed using Chebysev shifted polynomials, and linear identification in time domain based on measured glucose and insulin concentration values was applied. The glucose and insulin input functions have been approximated and the model parameters of IIC were estimated. This extended Bergman model suits considerably better to the practical clinical situation, and it can improve the effectivity of the external control design for glucose-insulin process. The IIC part has been identified via dynamical neural network using the proposed SOSI technique. The symbolic and numerical computations were carried out with *Mathematica* 5.1, and with its application Neural Networks 2.0.

Keywords: Glucose–insulin interaction, internal insulin control, identification, dynamic neural network, symbolic computation, *Mathematica*.

1. Introduction

Nowadays health experts refer to diabetes mellitus as the 'disease of the future'. The World Health Organization's (WHO) newest statistics show that 4% of the adult society of the world suffer from diabetes mellitus, and this value could increase to 5.4% by 2025. Van den Berghe [15, 16] has shown that tight glucose control can reduce the Intensive Care Unit (ICU) patient mortality by 45% if the glucose level is kept less than 6.1 mmol/L for a cardiac care population. It was shown that automated control algorithms capable of tight regulation for glucose intolerant ICU patients would reduce mortality, as well as the current burden on ICU medical resources and time.

To design an appropriate control, an adequate model is necessary. During the last 50 years, various models for the interaction between glucose and insulin have been suggested [1, 6, 9, 13, 14], but the benchmark model was the minimal model of Bergman [3]. Bergman's two compartment minimal model explains and evaluates in the simplest way the results of the intravenous glucose tolerance test (IVGTT).

However, the shortcoming is its big sensitive to variance in the parameters and that the plasma insulin concentration must be known as a function of time. Therefore, extensions of this minimal model have been proposed, [4, 10, 11] using even control algorithms [5], trying to capture the changes in patient dynamics of the glucose-insulin interaction, particularly with respect to insulin sensitivity.

Our researches have been focused on the optimization of the amount of insulin. The proposed modified Bergman model has kept the minimal model's properties [2, 7], and good results have been achieved [8, 12], but the shortcomings of the Bergman model remained.

This paper proposes an extension of the minimal model, but in a different way, than the mentioned works have done. We are adding an internal insulin control (IIC) part, representing the own insulin control of the human body by using mostly control theory and less physiological aspects. However, the obtained model is built by clinical experiments made on oral glucose intake tests, and measured at the Heim Pál Hospital for Sick Children from Budapest, proving the long-term applicability of our model.

The symbolic and numerical computations were carried out and presented as a live worksheet with *Mathematica* 5.1, and with its application Neural Networks 2.0.

2. Materials and Results

2.1. Model Equations

The original Bergman model consists of two well-known equations, [3]:

```
deq1 = X'[t] == p1X[t] + p2h[t];

deq2 = Y'[t] == (p3 - X[t])Y[t] + i[t] + p4;                    (1)
```

with the following parameters, [6]:

```
parameters = {p1 → -0.021151, p2 → 0.092551,
    p3 → -0.014188, p4 → 0.077947};                             (2)
```

The terms $h(t)$ and $i(t)$ stand for exogenous insulin and glucose as inputs of the system. $X(t)$ and $Y(t)$ are the concentration of glucose in the plasma and that of the insulin remote from plasma, respectively. In our case $X(t)$ and $Y(t)$ represent both the states and the output of the system, because the dynamic of the measurement and actuator devices are considerably faster than that of the system itself. The constants $p_i (i = 1, 2, \ldots, 4)$ are the model parameters.

We should like to extend this model in order to take into consideration an important phenomenon, the internal insulin control (IIC), namely the own insulin control of the body. We neither want to develop a new model nor estimate new values for parameters p_i of Bergman's model, just to add a new part, which considerably improves its applicability for real clinical situations.

Therefore, we tried to extend the minimal model with a third equation:

$$i_{int} = F(i_{int}, X(t), Y(t), h(t)) \tag{3}$$

where the insulin inlet $i(t)$ in the second equation of (1) is divided into an internal $i_{int}(t)$ and an external part $i_{ext}(t)$ (see *Fig. 1*):

$$i(t) = i_{int}(t) + i_{ext}(t) \tag{4}$$

In order to identify our suggested extension, the input and output signals of the model are needed. The clinical experiments were taken using oral glucose intake (OGI), instead of intravenous injection and only the values of $X(t)$ and $Y(t)$ were measured. Therefore, first the signals $i_{int}(t)$ and $h(t)$ should be computed from these measurements.

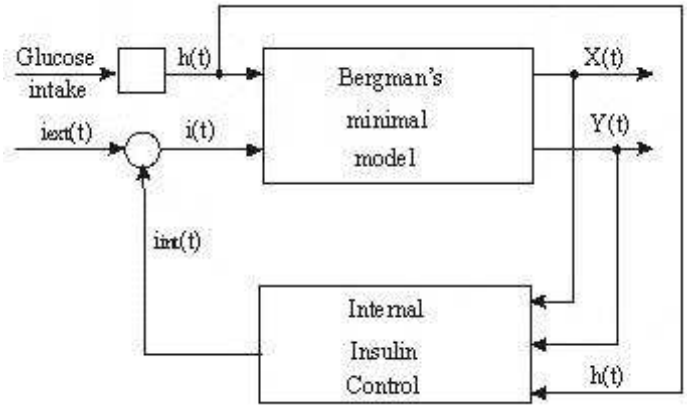

Fig. 1. The block diagram of the extended Bergman model.

2.2. *Theoretical Approach of Oral Glucose Intake*

In case of oral glucose intake – in contrast to intravenous glucose injection – it takes time while the glucose is absorbed in the stomach and the glucose concentration in the blood increases. The simplest model for this process is the perfectly mixed tank model with first order reaction,

$$V\frac{dX}{dt} = -kX. \tag{5}$$

Solving this equation with the initial condition $X(0) = X_0$,

$$X(t) = X_0 e^{-\frac{k}{V}t} \tag{6}$$

Then glucose inlet flux into the blood circuit is proportional with,

$$-\frac{dX}{dt} = X_0 \frac{k}{V} e^{-\frac{k}{V}t} \tag{7}$$

Consequently, the glucose influx in the Bergman model $h(t)$ can be expressed as

```
h[t_] := αe^-βt                                                    (8)
```

2.3. Estimation of the Parameters α and β

Now, the first equation of the Bergman model is:

```
deq1
```

$$X'\ t\ == \alpha e^{-\beta t}\alpha p_2 + p_1 X\ t \tag{9}$$

which can be solved with the initial condition:

```
ic1=X[0]==X0                                                       (10)
X[t_]=X[t]/.(DSolve[{deq1,ic1},X[t],t]//Simplify)[[1]]
```

$$\frac{e^{tp_1}(\beta X0 + p_1 X0 + (\alpha - e^{-t(\beta+p_1)}\alpha)p_2)}{\beta + p_1}$$

We have determined α and β parameters by clinical experiments using the oral glucose intake test as measurement method. At the Heim Pál Hospital for Sick Children from Budapest we have made tests on 14 different patients.

Oral glucose intake test known as oral glucose tolerance test (OGTT) is usually performed to verify diagnosis when diabetes is suspected but symptoms are absent. Data from an OGTT can be used to determine if an individual has an impaired glucose tolerance, which is a prerequisite for diabetes.

Patients should be drink in five minutes 2-3 dl water with maximum 75g glucose. After this, glucose level is measured at adults in two hours duration at each 30 minute. In children measurements are taken also 150 and 180 minutes after drinking the sugared water.

The estimation is presented over an oral glucose measurement set of a child (see *Fig. 2*):

```
glucosedata={0.,0.0432,0.0378,0.024,0.0234,0.009,0.};              (11)
```

```
times={0.,30.,60.,90.,120.,150.,180.};                             (12)
```

Employing our solution, the parameters α and β can be estimated on the bases of these measured values. Substituting the parameter values p_1 and p_2, we get:

```
model=X[t]/.parameters/.X0 → 0                                     (13)
```

$$\frac{0.092551e^{-0.021151t}(\alpha\ -\ e^{-t(-0.021151+\beta)}\alpha)}{\beta - 0.021151}$$

```
<< Statistics`NonlinearFit`                                        (14)

αβ =BestFitParameters/.NonlinearRegress[Transpose[{times,
    glucosedata}],model,t,{α, β}]
    {α → 0.0340007, β → 0.0322824}
```

```
model=X[t]/.αβ
```

$$8.31443e^{-0.021151t}(0.0340007 - -0.0340007e^{-0.0111314t})$$

Checking statistical significance it can be seen that the resulted model fits well the measured values (11) and (12):

```
NonlinearRegress[Transpose[{times,glucosedata}], model,t,{α, β}]
```
(15)

$$\{BestFitParameters \rightarrow \{\alpha \quad \rightarrow 0.0340007, \beta \rightarrow 0.0322824\}$$

2.4. Approximation of the Insulin inlet of Internal Insulin Control

In order to identify a model for IIC, first one needs to estimate the insulin influx produced by the internal insulin control. Therefore an inverse problem should be solved, namely, we know the model (now represented by the second equation of the Bergman model (1)) and the output (the measured values of the insulin concentration in time) exemplified by the same patient as in (11), but now for his insulin parameters:

```
insulindata={25.3, 91.2, 64.2, 73.5, 51.3, 37.4, 24.1};
```
(16)

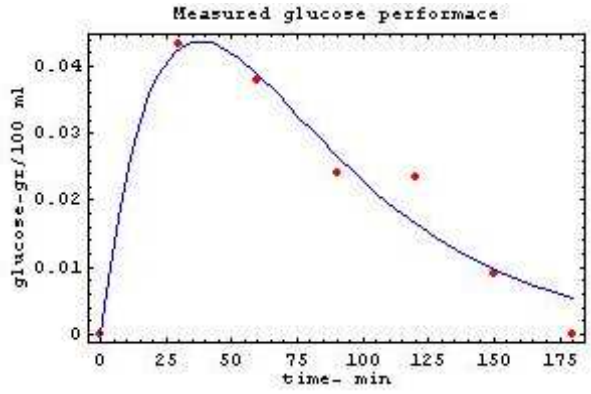

Fig. 2. The measured glucose values and the estimated model.

We are looking for the input, the insulin $i(t)$ function. In these experiments, no external insulin control took place, therefore $i(t) \equiv i_{int}(t)$. To solve this inverse problem for non-autonomous SISO system in form

```
y'(t) = a(t)y(t) + b(t)u(t) + c(t)
```
(17)

a numerical method has been developed (SOSI), which approximate the unknown $u(t)$ function (representing $i_{int}(t)$) with the linear combination of shifted Chebyshev polynomials (T_i), namely:

$$\mathtt{u(t)}=\sum_{i=0}^{n} \gamma_{\mathtt{i}}\ \mathtt{T_i}\left(2\tfrac{\mathtt{t}}{\theta}-1\right) \tag{18}$$

where these polynomials are valid in *[0, θ]* interval. The derivative of $y(t)$is approximated by a three point finite difference formula.

2.5. *Implementation of Function SOSI*

In the followings the realization of the SOSI module is presented. This is basically the implementation of the Chebyshev polynomials:

```
<<LinearAlgebra`MatrixManipulation`

SOSI[a_, b_, c_, tm_, xm_, n_] := Module[{m, Λ, i, t, x, u, eqs, A,
B, P, p},

m = Length[xm];

Λ= tm[[2]]-tm[[1]];

Do[t_i= iΛ, {i, 0, m-1}];

Do[x_i= xm[[i+1]], {i, 0, m-1}];

p = Table [z_i, {i, 0, n}]

u=Apply[Plus,Table[z_i Chebysev[i,2η/t_(m-1)-1],{i,0,n}]];

eqs = {t_2^2 (x_0 -x_1 )+ 2t_o (t_2 (-x_o +x_1) +t_1 (x_o -x_2 ))+
     +t_1^2 (-x_o +x_2)+t_o^2 (-x_1 +x_2)}/((t_o -t_1)(t_o -t_2)(t_1 -t_2) ==
     ==a[t_o]x_o +b[t_o ](u/.η → t_o)+c;

eqs=Join[{eqs},Table[(t_(1+i)^2(x_(-1+i) -x_i ) -
      -2t_i (t_(1+i) (x_(-1+i) -x_i)+t_(-1+i) (x_i -x_(1+i)))+
     +t_i^2 (x_(-1+i) -x_(1+i))+t_(-1+i)^2(x_i -x_(1+i)))/
     /((t_(-1+i) -t_i )(t_(-1+i) -t_(1+i) )(t_i -t_(1+i)))==
     == a[t_i]x_i +b[t_i](u/.η → t_i)+c,{i,1,m-2}]];

eqs=Append[eqs,(t_(-1+m)^2 (-x_(-3+m) +x_(-2+m)) -
      -2t_(-2+m)t_(-1+m) (x_(-3+m)-x_(-1+m))+t_(-3+m)^2 (x_(-2+m) -x_(-1+m))+
     +t_(-2+m)^2(-x_(-3+m) +x_(-1+m))+2t_(-3+m)t_(-1+m)(-x_(-2+m) +x_(-1+m)))/
     /((t_(-3+m)-t_(-2+m))(t_(-3+m)-t_(-1+m))(t_(-2+m)-t_(-1+m) ))==
     ==a[t_(m-1)]x_(m-1)+b[t_(m-1)](u/.η → t_(m-1))+c];

{A, B}= LinearEquationsToMatrices[eqs,p];

P=PseudoInverse[A];
```

```
p=P.B
```

$$\sum_{i=1}^{n+1} \texttt{p[[i]]ChebysevT[i-1,}\frac{2\eta}{t_{m-1}}\texttt{-1]}$$

Applying the SOSI algorithm on the glucose-insulin model we have got:

$$\texttt{a[t\_] = (p}_3\texttt{ -- X[t]) /. parameters /.}\alpha\beta\texttt{) /. X0 }\rightarrow\texttt{0} \qquad (19)$$
$$-0.014188 - 8.31443e^{-0.021151t}(0.0340007 - 0.0340007e^{-0.0111314t})$$

$$\texttt{b[t\_]=1;} \qquad (20)$$

$$\texttt{c = p}_4\texttt{ /.parameters}$$
$$0.077947$$

For SISO input we need to generate artificial measurements using spline interpolation (see *Fig. 4*), because we need to estimate the γ_i parameters ($i = 0 \ldots n$) of the shifted Chebyshev polynomials, (6). Results are presented in *Fig. 4* illustrating the approximation of the input inlet insulin flux generated by IIC.

By using the computed $i(t)$ function, the second equation of the Bergman model can be solved only by numerical integration with the initial condition *Y[0] = 25.3 $\mu U/$*(kg min) (see (16)). The obtained solution gave us the same interpolation as in *Fig. 3* and it corresponds also to the open loop simulation test of the insulin.

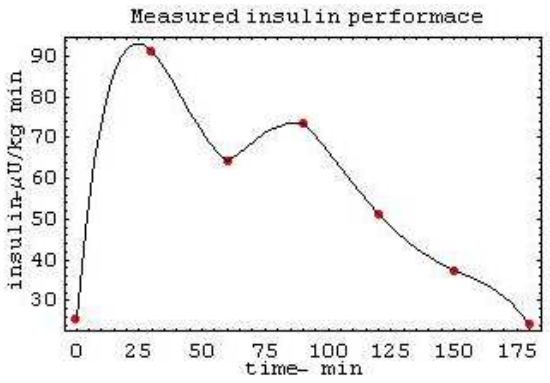

Fig. 3. The interpolated measured insulin values.

2.6. Identification of IIC Model via Dynamic Neural Network

Now having the output $i_{int}(t)$ and the inputs $X(t)$, $Y(t)$ and $h(t)$ of IIC a dynamic neural network can be built to identify the IIC model. As input function we have used the previously calculated α and β values:

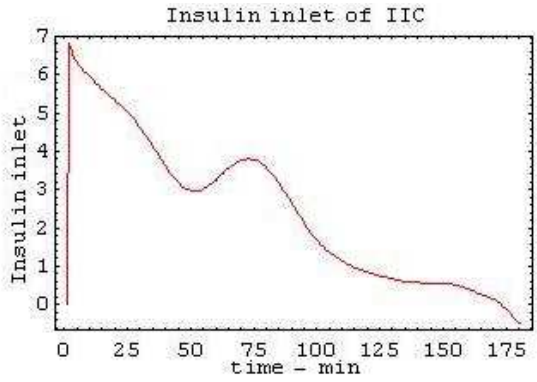

Fig. 4. The insulin inlet flux generated by IIC.

```
h[t]/.αβ
```
$$0.0340007e^{-0.0322824t} \tag{21}$$

Therefore, the equation for $i_{\mathrm{int}}(t)$ is (see *Fig. 1*):

```
iint[t] =F[iint[t-1],X[t],Y[t],h[t],X[t-1],Y[t-1],h[t-1]]
```
(22)

Consequently, the dynamical neural network of IIC has been built as follows:

```
<<NeuralNetworks‘

y=Table[{i[t]},{t,0,180}];

u=Table[{Xint[t],Yint[t],h[t]/.αβ},{t,0,180}];

{model1,fitrecord}=NeuralARXFit[u,y,{{1},{2,2,2},
     {0,0,0}},FeedForwardNet,{1},CriterionPlot → False,
     RandomInitialization → LinearParameters,
     Regularization → 0.0001];
```

As a result the estimated internal insulin regulator nonlinear model in discrete form is:

```
model1[[1]][{y[t-1],u1[t],u2[t],u3[t],u1[t-1],u2[t-1],u3[t-1]}]
```
(23)
$$-3.46165 + 10.671/(1 + e^{0.935576t+0.269209u1\ -1+t\ -3.71082u1\ t}\cdot e^{-3.8279u2\ -1+t\ -2.87889u2\ t\ -3.46827u3\ -1+t\ -0.278068u3\ t}\cdot e^{-0.195113y\ -1+t}\ )$$

Results show (see *Fig. 5*) that in the obtained model the insulin variation could describe not only critical care situation, but it fits well also the interstitial insulin (two peaks in the insulin response). Therefore, we improved the minimal model proposed by Bergman.

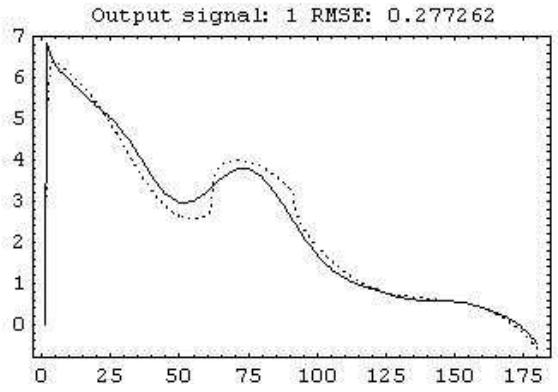

Fig. 5. Comparison between the insulin inlet flux generated by IIC and by Dynamic Neural Network.

3. Conclusion

In this paper we proposed an extension of the minimal model, based on control theory aspects and we have validated it based on clinical experiments. We would like to point out that we didn't develop a new model or estimate new values for parameters p_i of Bergman's model, but just added a new part, the internal insulin control (IIC) part, representing the own insulin control of the human body.

The advantage of this model is that insulin variation could describe not only critical care situation, but it fits well also the interstitial insulin and not only the insulin in a remote compartment as proposed by Bergman.

Statistical parameters gave good results, also demonstrated by the insulin inlet flux generated by Dynamic Neural Network.

As a result we believe that after further verifications the model could provide a useful help to control the blood glucose level, and in the optimization process of diabetic administration.

4. Acknowledgements

This research has been supported by the Hungarian National Research Fund, Grants No. F046726 and T042990.

I would like to express special thanks to Béla Paláncz for the help he gave me in using Mathematica and to Piroska Simonné-Sebestyén who helped me in collecting the measurements.

References

[1] BENETT, D. L.–GOURLEY, S. A., Asymptotic Properties of a Delay Differential Equation Model for the Interaction of Glucose with Plasma and Interstitial Insulin, *Elsevier, Applied Mathematics and Computation,* **151/1** (2003), pp. 189–207.

[2] BENYÓ, B.–BENYÓ, Z.–PALÁNCZ, B.–KOVÁCS, L.–SZILÁGYI, L., A Fully Symbolic Design and Modelling of Nonlinear Glucose Control with Control System Professional Suite (CSPS) of Mathematica, Proc. of the World Congress on Medical Physics and Biomedical Eng. Sydney, Australia, 2003, #2813, Available: http://library. wolfram.com/infocenter/Mathsource/5043.

[3] BERGMAN, B. N.–IDER, Y. Z.–BOWDEN C. R.–COBELLI C., Quantitive estimation of insulin sensitivity. *American Journal of Physiology,* **236** (1979), pp. 667–677.

[4] FERNANDEZ, M.–ACOSTA, D.–VILLASANA, M.– STREJA, D., Enhancing Parameter Precision and the Minimal Modeling Approach in Type I Diabetes, *Proc. of 26th Ann. Int. Conf. of IEEE Eng. in Biomedicine Soc.*, September 2004, San Francisco, CA, USA, pp. 797–800.

[5] HOVORKA, R.–CANONICO, V.–CHASSIN, L. J.–HAUETER, U.–MASSI-BENEDETTI, M.–ORSINI FEDERICI, M.–PIEBER, T. R.–SCHALLER, H. C.–SCHAUPP, L.–VERING, T.–WILINSKA, M. E., Nonlinear Model Predictive Control of Glucose Concentration in Subjects with Type 1 Diabetes, Physiological Measurement, **25** (2004), pp. 905–920.

[6] JUHÁSZ, CS., *Medical Application of Adaptive Control Supporting Insulin Therapy in case Of Diabetes mellitus*, Ph.D. dissertation, electrical eng. program, Budapest University of Technology and Economics, Budapest, Hungary, 1993.

[7] KOVÁCS, L.–PALÁNCZ, B., Linear and Nonlinear Approach of the Glucose-Insulin Control using Mathematica, *Periodica Polytechnica Trans. On Automatic Control and Computer Science Timisoara Romania,* **49/63** (2004), pp. 65–71.

[8] KOVÁCS, L.–PALÁNCZ, B.–ALMÁSSY, ZS.–BENYÓ, Z., Optimal Glucose-Insulin Control in H_2 space, Proc. of 26th Ann. Int. Conf. of IEEE Eng. in Biomedicine Soc., September 2004, San Francisco, CA, USA, pp. 762–765.

[9] LEHMANN, E. D.–DEUTSCH, T., Compartmental Models for Glycaemic Prediction and Decision Support in Clinical Diabetes Care: Promise and Reality, *Elsevier, Computer Methods and Programs in Biomedicine,* **56** (1998), pp. 193–204.

[10] LIN, J.–CHASE, J. G.–SHAW, G. M.–DORAN, C. V.–HANN, C. E.–ROBERTSON, M. B.–BROWNE, P. M.–LOTZ, T.–WAKE G. C.–BROUGHTON, B.: Adaptive Bolus-Based Set-Point Regulation of Hyperglycemia in Critical Care, *Proc. of 26th Ann. Int. Conf. of IEEE Eng. in Biomedicine Soc.*, September 2004, San Francisco, CA, USA, pp. 3463–3466.

[11] MORRIS, H. C. – O'REILLY, B. – STREJA, D., A New Biphasic Minimal Model, *Proc. of 26th Ann. Int. Conf. of IEEE Eng. in Biomedicine Soc.*, September 2004, San Francisco, CA, USA, pp. 782–785.

[12] PALÁNCZ, B.–KOVÁCS, L., Application of Computer Algebra for Glucose-Insulin Control in H2/Hinf Space Using Mathematica, *Periodica Polytechnica Budapest*, in press, 2005.

[13] STURIS, J.–POLONSKY, K. S.–MOSEKILDE, E.–VAN CAUTER, E.: Computer Model for Mechanisms Underlying Ultradian Oscillations of Insulin and Glucose, *American Journal of Physiology,* **260** (1991), pp. 439–445.

[14] TOLIC, I. M.–MOSEKILDE, E.–STURIS, J., Modeling the Insulin Glucose Feedback System: Signification of Pulsatile Insulin Selection, *Journal of Theoretical Biology,* **3/1** (2000), pp. 361–375.

[15] VAN DEN BERGHE, G.: Insulin Therapy for the Critically Ill Patient, *Clinical Cornerstone*, **5/2** (2003), pp. 56–63.

[16] VAN DEN BERGHE, G.–WOUTERS, P.–WEEKERS, F.– VERWAEST, C.–BRUYNINCKX, F.–SCHETZ, M.–VLASSELAERS, D.– FERDINANDE, P.–LAUWERS, P.–BOUILLON, R.: Intensive Insulin Therapy in Critically Ill Patients, *New England Journal of Medicine*, **345/19** (2001), pp. 1359–1367.