Stuck in Modelling – Attempts to describe disease progress and the action of oral hypoglycaemic agents in type 2 diabetes

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Pathophysiology of Type 2 Diabetes

ADIAGNOSIS

Insulin levels
Insulin sensitivity
β-cell Failure

Post-Meal glucose
Fasting glucose

Obesity IGT Diabetes Uncontrolled hyperglycemia

IGT = Impaired Glucose Tolerance
Adapted from: Type 2 Diabetes BASICS. Minneapolis, MN: International Diabetes Center, 2000.
Four Possible Anti-Diabetic Mechanisms

• Beta Cell Function
  – Insulin production
  – ‘Offset’ increased insulin secretion
  – ‘Slope’ decreased rate of loss of beta function

• Insulin “Sensitivity” (potency)
  – Insulin pharmacodynamics (‘insulin effect’)
  – ‘Offset’ increased insulin potency
  – ‘Slope’ decreased rate of loss of potency

Note: insulin may slow glucose production and/or increase elimination

Insulin-Glucose Homeostasis
Mechanism-based model structure

Pharmacodynamic Model

Offset Parameters
- OBF = CEBFT + EOBFC
- OIP = CEIPT + EOIPC

Slope Parameters
- SBF = (ESBFT + ESBFC)
- SIP = (ESIPT + ESIPC)

Offset Effect
- BF(c) = BF(t) * (1 + OBF)
- IP(c) = IP(t) * (1 + OIP)

Slope Effect
- \( \frac{d}{dt}(BF) = KBF \times (1 + SBF) \times BF(t) \)
- \( \frac{d}{dt}(IP) = KIP \times (1 + SIP) \times IP(t) \)

Glucose-Insulin Homeostasis

- Glucose and Insulin are part of a coupled feedback system
- Several models have been proposed for this regulation e.g.
  - Some very simple (Oxford HOMA)
  - Some more realistic (Uppsala)
  - Some very complex (Chicago)
The Problem

• Insulin (half-life 4 mins) and glucose (half-life 30 mins) respond rapidly to changes in beta cell function or insulin potency
• Beta cell function (BF) and Insulin potency (IP) changes are slow (half-life at least 2 weeks with gliclazide)
• Disease follow up is 2 years
• Stiff system of differential equations

• VERY SLOW – Run times of weeks to months

A Solution – Part 1

• Assume Glucose and Insulin reach homeostatic equilibrium instantly
  – No need for 2 DES with very fast turnover
  – Still requires 4 DES for disease progress and effect compartments
• How to solve for glucose and insulin?
$AES$

CEBFT=A(3)  
CEIPT=A(4) 
; Offset Drug Effect
OBF=(CEBFT+EOBFC)*PPVOBF
OIP=(CEIPT+EOIPC)*PPVOIP
EBFUN=A(1)*(1+OBF)
EIPOT=A(2)*(1+OIP)

EINS=A(5)/VINS ; Insulin Conc
EGLU=A(6)/VGLU ; Glucose Conc

IFBG=EINS ; Insulin Feedback
GFBI=EGLU-GLUSTD ; Glucose Feedback

$ERROR$

; Steady State Solution
FSI=A(5)
FSG=A(6)

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$AES$

ECEBFT=A(3) ; BF Treatment effect
ECEIPT=A(4) ; IP Treatment effect
; Offset Drug Effect
EOBF=(ECEBFT+EOBFC)*PPVOBF ; Beta Cell Function
EOIPC=(ECEIPT+EOIPC)*PPVOIP ; Insulin Potency

EBFUN=A(1)*(1+EOBF)
EIPOT=A(2)*(1+EOIPC)

EINS=A(5)/VINS ; Insulin Conc
EGLU=A(6)/VGLU ; Glucose Conc

GFBG=(EGLU/GLUSTD)**GPRG ; Glucose Feedback on Glucose
GFBI=(EGLU/GLUSTD)**IPRG ; Glucose Feedback on Insulin

E(5)=RINS*EBFUN*GFBI - CLINS*EINS ; dIns/dt
E(6)=RGLU/(EIPOT*IFBG) - CLG+CLGI*EINS*EIPOT*EGLU ; dGlu/dt

$ERROR$

; Steady State Solution
FSI=A(5)
FSG=A(6)
Chicago Model

$AES

ECEBFT=A(3) ; RF Treatment effect
ECEIPT=A(4) ; IP Treatment effect
EOBF=(ECEBFT+EOBFC)*PPVOBF
EOIP=(ECEIPT+EOIPC)*PPVOIP

EBFUN=A(1)*(1+EOBF) ; Beta cell function
EIPOT=A(2)*(1+EOIP) ; Insulin potency

Z=A(5) ; Amount Glucose mg
X=A(6) ; Amount Insulin in Central Cpt mU
XE=A(7) ; Amount Insulin in Peripheral Cpt mU
H3=X ; Amount Insulin in Effect Cpt mU

F1Z=RINSMU/(1+EXP(-Z/(300*V3)+6.6)) ; RinInsGLuDep mU/min
F2Z=72*(1-EXP(-Z/(144*V3))) ; RoutGluIndep mg/min
F4Y=90/(1+EXP(-1.772*LOG(EIPOT*XE*(1/V2+1/(EINS*T2)))+7.76))+4 ; KGluInsDep 1/min
I=RGLUMG*216/(216+180) ; RinGluIndep mg/min
F5H3=RGLUMG*180/(216+180)/(1+EXP(0.29*H3*EIPOT/V1 - 7.5)) ; RinGluInsulinDep mg/min

E(5)=F1Z*EBFUN - EINS*(X/V1 - XE/V2) - X/T1 ; dIns/dt mU/min
E(6)=F5H3 + I - F2Z - F3Z*F4Y ; dGlu/dt mg/min
E(7)=EINS*(X/V1 - XE/V2) - XE/T2 ; dPeripheralIns/dt mU/min

But …

• Run times still very slow with $AES
  – steady state solution is computed every
time $DES is evaluated?

• More complex models (Uppsala, Chicago) cause numerical solution
difficulties for NONMEM

OCCURS DURING SEARCH FOR ETA AT INITIAL VALUE, ETA=0
ERROR IN LSODI1: CODE 205
ERROR OCCURRED WHILE ATTEMPTING TO OBTAIN INITIAL VALUES FOR ATOL
PROGRAM TERMINATED BY OBJ
MESSAGE ISSUED FROM ESTIMATION STEP
AT INITIAL OBJ. FUNCTION EVALUATION
Oxford Model (HOMA) 
Quadratic Solution

AX=1
BX=-GLUSTD
CX=-CLINS*RGLU/(IP*BF*CLGLU*RINS)

; Steady State Solution
FPG=(-BX + SQRT(BX*BX - 4*AX*CX))/(2*AX)
FSI=RINS*BF*(FPG-GLUSTD)/CLINS

Challenges

• HOMA system is simple to solve but not well accepted as a physiological model
• Models take weeks to run
• Hard to evaluate alternative models
• Impractical to get estimates of parameter uncertainty
A Solution – Part 2

• Assume BF, IP and Ce are constant from one TIME to the next
  – Crude Euler like solution to differential eqn
  – Not different from DES solution in practice using monthly observation records
  – Run times 400x faster!
  – Can MTIME be used?
  – How to access TIME when using MTIME?
• Only practical for HOMA quadratic SS solution

A Solution – Part 3

• Use Parallel Thread Computing Model
  – Perform calculations for many individuals I parallel instead of sequentially
  – Use all available cores/CPUs one machine or on computing grid
  – S-ADAPT with MCPEM
    • Juergen Bulitta at SUNY has this system working
A Solution – Part 4