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

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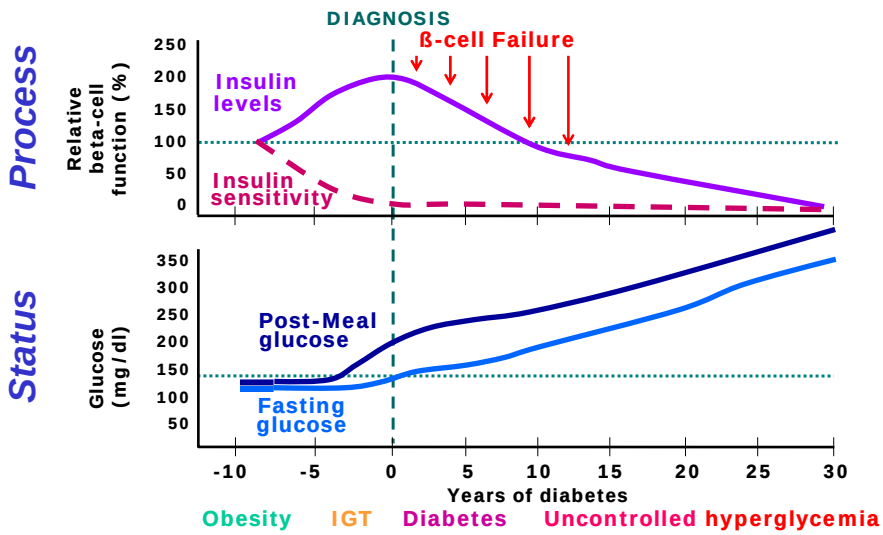
Pathophysiology of Type 2 Diabetes



IGT = Impaired Glucose Tolerance

Adapted from: *Type 2 Diabetes BASICS*. Minneapolis, MN: International Diabetes Center, 2000.

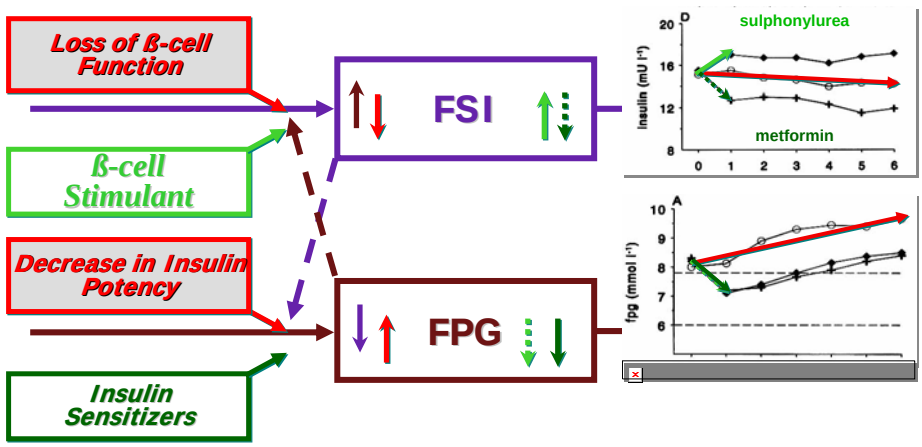
Four Possible Anti-Diabetic Mechanisms

- 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

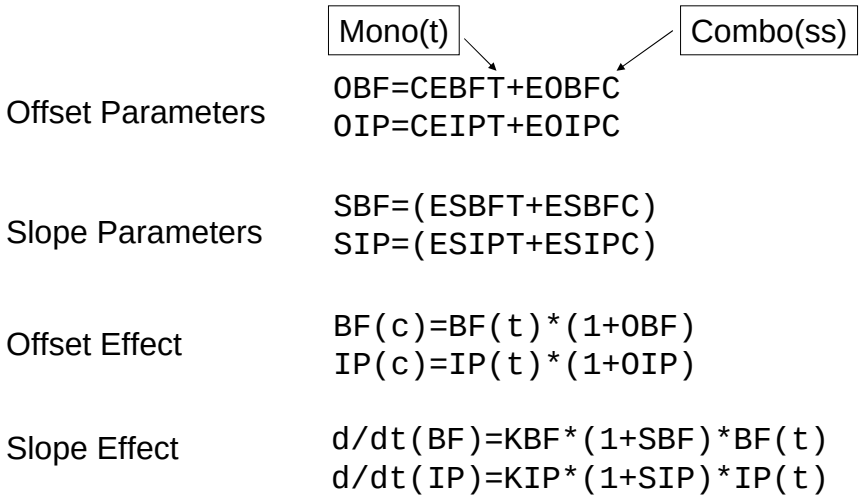
Note: insulin may slow glucose production and/or increase elimination

Insulin-Glucose Homeostasis
Mechanism-based model structure



De Winter et al. J.Pharmacokin. Pharmacodyn.; Jun;33(3):313-43. (2006)

Pharmacodynamic Model



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?

Oxford Model (HOMA) Algebraic Equations

```
$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

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

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


Uppsala Model

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

   EBFUN=A(1)*(1+EOBF)
   EIPOT=A(2)*(1+EOIP)
   EINS=A(5)/VINS ; Insulin Conc
   EGLU=A(6)/VGLU ; Glucose Conc
   GFBG=(EGLU/GLUZ)**GPRG ; Glucose Feedback on Glucose
   GFBI=(EGLU/GLUZ)**IPRG ; Glucose Feedback on Insulin

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

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

Chicago Model

```
$AES
   ECEBFT=A(3) ; BF Treatment effect
   ECEIPT=A(4) ; IP Treatment effect
   ;Offset Drug 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
   F3Z=0.01*Z/V3                   ; RoutGluFirstOrder mg
   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 OCURRED WHILE ATTEMPTING TO OBTAIN INITIAL VALUES FOR ATOL
0PROGRAM 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