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Appendix A. Binding Affinity (K_D) Values: Least Squares Analysis

Least squares analysis is a distributed error approximation method. This involves the decrease of some global error measure with respect to the whole approximation interval as the order of approximation increases. It is valuable in fitting equations to discrete data points and in analyzing measurement errors.

Based on an form of the equation:

$$y_p(x_i) = aC_1 + C_2,, \quad (1)$$

the least squares procedure forms the sum of the squares of the differences between observed values (y_i) and the predicted values $y_p(x_i)$. The equation is minimized with respect to the unknown parameters C_1 and C_2. Therefore, a normalized error quantity predicts the goodness of fit of the data to the model.

$$\text{Error} = \sum_{i=1}^{N} [y_i - (aC_1 + C_2)]^2 / (N-p), \quad (2)$$

where N = number of data points; p = number of parameters to be considered.

Error is minimized with respect to C_1 and C_2 by using:

$$0 = \delta\text{Error} / \delta C_1 = \sum_{i=1}^{N} [y_i - (aC_1 + C_2)], \quad (3)$$

$$0 = \delta\text{Error} / \delta C_2 = \sum_{i=1}^{N} [y_i - (aC_1 + C_2)]x_i^k. \quad k= 0,1... \quad (4)$$

Expansion of the sums generates two linear algebraic equations for the coefficients C_1 and C_2. Once the parameters are known, error can be determined[75].

Time derivatives describing the bound complex of IGF-I (I) and IGFBP-3 (BP) or p9 HS (PG) were established. The time derivative for the IGF-1 / IGFBP-3 complex (B) is as follows:

$$dB / dt = k_{on}^{s}[I][BP] - k_{off}^{s}[B], \qquad (5)$$

where $I = I_o - B$, $BP = BP_o - B$. At steady state the rate of change of the IGF-I / IGFBP-3 complex (B) is zero and Equation 5 becomes:

$$I_o = K_D^{s}[B] / [BP_o - B] + [B], \qquad (6)$$

where $K_D^{s} = k_{off}^{s} / k_{on}^{s}$. Equation 6 becomes y "predicted" (Equation 1) with $I_o = y_p$, K_D = a, $B / [BP_o\text{-}B] = C_1$ and $[B] = C_2$. Least squares analysis from experimental assay data yielded K_D values of 6.2×10^{-9} M for the biodot assay and 3×10^{-9} M for the charcoal assay. As discussed in Chapter III.A and B, the charcoal assay was the preferable assay for quantitating binding affinity.

Likewise, a time derivative describing the rate of change of the IGF-I / p9 HS complexes (P) is:

$$dP / dt = k_{on}^{p}[I][PG] - k_{off}^{p}[P], \qquad (7)$$

where $I = I_o - P$, $PG = PG_o - P$. At steady state the rate of change of IGF-I / p9 HS complex (P) is zero and Equation 7 becomes:

$$I_o = K_D^{p}[P] / [PG_o - P] + [P], \qquad (8)$$

where $K_D^{p} = k_{off}^{p} / k_{on}^{p}$. Equation 8 becomes y "predicted" (Equation 1) with $I_o = y_p$, K_D = a, $P / [PG_o\text{-}P] = C_1$ and $[P] = C_2$. Least squares analysis from experimental assay data yielded K_D values of 2.2×10^{-7} M for the biodot assay and 1.5×10^{-8} M for the charcoal assay.

Appendix B. BAE Cell System Model FORTRAN Codes

Basic BAE Cell System Model:

```
C
C**************************** ABSTRACT
*******************************
C
C    THIS PROGRAM APPLIES THE  LIBRARY ROUTINE LSODE TO THE
C  INTEGRATION ON A NON-STIFF SET OF ODE'S.  NOMENCLATURE FOR THIS
C  PROGRAM CAN BE FOUND IN FILE LSDP1.
C
C*******************************************************************
C
c    Basic BAE Cell- Y(1) = u (dimensionless unbound receptors, R/Ro)
c                  - Y(2) = v (dimensionless bound receptors, C/Ro)
c                  - Y(3) = y (dimensionless ligand, Lo/Kd)
c                   initial conditions:       Y(1) = 1
c                                             Y(2) = 0
c                                             Y(3) = Lo/Kd
C    integrate from zero time (t=0) to 3 hours (t=10800 secs)
c
     IMPLICIT REAL*8(A-H,O-Z)
C   NONSTIFF PROBLEMS (MF = 10)
C   RWORK(20+16*NEQ), IWORK(20)
C   DIMENSION Y(3),ATOL(3),RWORK(52),IWORK(20)
C
C   STIFF PROBLEMS (MF=21(WITH JACOBIAN),22(WITHOUT JACOBIAN)
C   RWORK(22+9*NEQ+NEQ**2),IWORK(20+NEQ)
    DIMENSION Y(3), ATOL(3),RWORK(58),IWORK(22)
C
C   NONSTIFF PROBLEMS/STIFF (MF=22)
C   EXTERNAL FEX
C   STIFF PROBLEMS (MF=21)
    EXTERNAL FEX,JAC
C
     common/class/b,rho
c    Parameter values
     Ro = 2d4
c    Ro = # of receptors/cell
```

```
      xkd = .6d-9
c     Kd= koff/kon = affinity of ligand to receptor = M
      a = 5.0d-4
c     a = radius of a single cell = cm
      D = 5.0d-7
c     D = diffusivity of ligand through binding buffer = cm2/s
      xkon = 4.0d7
c     kon = association rate constant for ligand and receptor = M-1s-1
      xLo = 5.7E-10
c     Lo = initial ligand concentration=M
      V=3.33d-5
c     V = binding buffer volume/avg. # of cells (15,000) = cm3
      xN=6.023d23
c     N = Avogadro's number = # sites/mol
C
C    Dimensionless Groups
      b = xkon*Ro*1000/(4.0d0*3.1416d0*a*D*xN)
c     [(L/mol*s)*(#/cell)*(L/1000 cm3)]/[(cm/cell)*(cm2/s)*(#/mol)]
      rho = (Ro*1000)/(V*xkd*xN)
c     [(#/cell)*(1000cm3/L)]/[(cm3)*(mol/L)*(#/mol)]
      write(*,*) b,rho
C   INITIAL CONDITIONS
      Y(1)=1.0d0
      Y(2)=0.0d0
      Y(3)=xlo/xkd
      Tin=0.0d0
      Tout =10.8d3
      Tin=tin*xkd*xkon
      Tout=Tout*xkd*xkon
      N = 100
      deltax =(tout-tin)/float(N)
C  DGEAR PARAMETER SPECIFICATIONS
      NEQ=3
      RTOL=1.E-6
      ITOL=1
      ATOL(1)=1.E-6
      ITASK=1
      ISTATE=1
      IOPT=0
C    nonstiff integrator
C    MF=10
C    LRW = 20*16*NEQ
```

```
C   LIW = 20
c    stiff integrator with jacobian
      MF = 21
      LRW = 22+9*NEQ+NEQ**2
      LIW = 20+NEQ
C  INTEGRATE IN EQUALLY SPACED SEGMENTS USING A DO-LOOP
     DO 10 K=1,N
     Tout=Tin+deltax
     CALL LSODE(FEX,NEQ,Y,Tin,Tout,ITOL,RTOL,ATOL,ITASK,ISTATE,IOPT,
     1RWORK,LRW,IWORK,LIW,JAC,MF)
C  PRINT OUT RESULTS
        WRITE(6,12) Tout/(xkd*xkon),Y(1),Y(2),Y(3)
        OPEN(Unit=95,FILE='BAE.DAT',STATUS='OLD')
        WRITE(95,22) Tout/(xkd*xkon),Y(1),Y(2),Y(3)
       tin=tout
 10   continue
 12   FORMAT( 14X,2HX=,G8.3,2X,5HY(1)=,D11.6,2X,5HY(2)=,D11.5,
                 2X,5HY(3)=,E14.2)
 22   FORMAT( E14.6,E14.6,E14.6,E14.6)

        STOP
      END
C
C*********************** SUBROUTINE FCN
********************************
C
C    THIS SUBROUTINE CALCULATES THE DERIVATIVE OF EACH DEPENDENT
C  VARIABLE WITH RESPECT TO X, YPRIME(I).
C
C*******************************************************************
C
      SUBROUTINE FEX(N,X,Y,YPRIME)
      IMPLICIT REAL*8(A-H,O-Z)
      INTEGER N
      DIMENSION Y(3),YPRIME(3)
      common/class/b,rho
      YPRIME(1)=(y(2)-y(3)*y(1))/(1.0d0+b*y(1))
      YPRIME(2)=(y(3)*y(1)-y(2))/(1.0d0+b*y(1))
      YPRIME(3)= ((-y(3)*rho*y(1) + rho*y(2))/(1.0d0+b*y(1)))
      RETURN
      END
C
```

```
C***************************  SUBROUTINE FCNJ
************************
C
C     THIS IS A DUMMY SUBROUTINE IF MF IS EQUAL TO 10/22 AND THE
C  JACOBIAN IS ESTIMATED NUMERICALLY.
C
C*******************************************************************
C
      SUBROUTINE JAC(N,X,Y,ML,MU,PD,NRPD)
      IMPLICIT REAL*8(A-H,O-Z)
      REAL*8 Y(3),PD(NRPD,3),X
      common/class/b,rho
c
      pd(1,1) =  ((-b*(y(2)-y(3)*y(1)))/((1.0d0+b*y(1))*(1.0d0+b*y(1))))-
                 (y(3)/(1.0d0+b*y(1)))
      pd(1,2) = 1.0d0/(1.0d0+b*y(1))
      pd(1,3) = -y(1)/(1.0d0+b*y(1))
      pd(2,1) =  ((b*(y(2)-y(3)*y(1)))/
                 ((1.0d0+b*y(1))*(1.0d0+b*y(1))))+(y(3)/(1.0d0+b*y(1)))
      pd(2,2) = -1.0d0/(1.0d0+b*y(1))
      pd(2,3) = y(1)/(1.0d0+b*y(1))
      pd(3,1) =  ((rho*b*(y(3)*y(1)-y(2)))/
                 ((1.0d0+b*y(1))*(1.0d0+b*y(1))))-(y(3)*rho/
                 (1.0d0+b*y(1)))
      pd(3,2) = rho/(1.0d0+b*y(1))
      pd(3,3) = (-rho*y(1)/(1.0d0+b*y(1)))
      RETURN
      END
```

IGF-I/IGFBP-3 BAE Cell System Model:

```
C
C***************************** ABSTRACT
********************************
C
C    THIS PROGRAM APPLIES THE  LIBRARY ROUTINE LSODE TO THE
C  INTEGRATION ON A NON-STIFF SET OF ODE'S.  NOMENCLATURE FOR THIS
C  PROGRAM CAN BE FOUND IN FILE LSDP1.
C
C*********************************************************************
C   IGF-I/IGFBP-3 BAE Cell System Model
c                      - Y(1) = u (dimensionless unbound receptors, R/Ro)
c                      - Y(2) = v (dimensionless bound receptors, C/Ro)
c                      - Y(3) = y (dimensionless ligand, Lo/Kd)
c                      - Y(4) = w (dimensionless unbound IGFBP-3, S/So)
c                      - Y(5) = z (dimensionless bound IGFBP-3, X/So)
c              IGFBP-3                  pick Kons = 4 x 10+7 M-1s-1
c                                       K_Ds = 3 x 10-9 M
c     initial conditions:               Y(1) = 1
c                                       Y(2) = 0
c                                       Y(3) = Lo/Kd
c                                       Y(4) = 1
c                                       Y(5) = 0
C     integrate from zero time (t=0) to 3 hours (t=10800 secs)
c
      IMPLICIT REAL*8(A-H,O-Z)
C     NONSTIFF PROBLEMS (MF = 10)
C     RWORK(20+16*NEQ), IWORK(20)
C     DIMENSION Y(5),ATOL(5),RWORK(100),IWORK(20)
C
C     STIFF PROBLEMS (MF=21(WITH JACOBIAN),22(WITHOUT JACOBIAN)
C     RWORK(22+9*NEQ+NEQ**2),IWORK(20+NEQ)
      DIMENSION Y(5), ATOL(5),RWORK(92),IWORK(22)
C
C     NONSTIFF PROBLEMS/STIFF (MF=22)
C     EXTERNAL FEX
C     STIFF PROBLEMS (MF=21)
      EXTERNAL FEX,JAC
C
      common/class/b,rho,alpha,beta,gamma
```

```
c  Parameter values
     Ro = 2.0d4
c      Ro=# receptors/cell
     xkd = .6d-9
c      Kd = koff/kon = affinity of ligand to receptor =M
     a = 5.0d-4
c      a = radius of a single cell
     D = 5.0d-7
c      D = diffusivity of ligand through binding buffer = cm2/s
     xkon = 4.0d7
c      kon = association rate constant for ligand and receptor = M-1s-1
     xLo = 5.7d-10
c      Lo = initial ligand concentration =M
     V=3.33d-5
c      V = binding buffer volume/avg. # of cells (15,000) = cm3
     So=2.8d-9
c      So = exogenous IGFBP-3 added = M
     xkons=4.0d7
c      kons = association rate constant for ligand and IGFBP-3 = M-1s-1
     xkds=3d-9
c      Kds = affinity of ligand to IGFBP-3 = M
     xN = 6.023d23
c      N = Avogadro’s # = #/mol
C     dimensionless groups
     b = xkon*Ro*1000/(4.0d0*3.1416d0*a*D*xN)
c      [(L/mol*s)*(#/cell)*(L/1000cm3)]/[(cm/cell)*(cm2/s)*(#/mol)]
     rho = (Ro*1000)/(V*xkd*xN)
c      [(#/cell)*(1000cm3/L)]/[(cm3*(mol/L)*(#/mol)]
     alpha = xkds/xkd
c      [M/M]
     beta = xkons/xkon
c      [(M-1s-1)/(M-1s-1)]
     gamma = So/xkd
c        [M/M]
     write(*,*) b,rho,alpha,beta,gamma
C  INITIAL CONDITIONS
     Y(1)=1.0d0
     Y(2)=0.0d0
     Y(3)=xlo/xkd
     Y(4)=1.0d0
     Y(5)=0.0d0
     Tin=0.0d0
```

```
      Tout =10.8d3
      Tin=tin*xkd*xkon
      Tout=Tout*xkd*xkon
      N = 100
      deltax =(tout-tin)/float(N)
C  DGEAR PARAMETER SPECIFICATIONS
      NEQ=5
      RTOL=1.E-6
      ITOL=1
      ATOL(1)=1.E-6
      ITASK=1
      ISTATE=1
      IOPT=0
C
c      nonstiff integrator
C        MF=10
C        LRW = 20*16*NEQ
C        LIW = 20
c      stiff integrator with jacobian
      MF = 21
      LRW = 22+9*NEQ+NEQ**2
      LIW = 20+NEQ
C  INTEGRATE IN EQUALLY SPACED SEGMENTS USING A DO-LOOP
      DO 10 K=1,N
        Tout=Tin+deltax
        CALL LSODE(FEX,NEQ,Y,Tin,Tout,ITOL,RTOL,ATOL,ITASK,ISTATE,IOPT,
     &            RWORK,LRW,IWORK,LIW,JAC,MF)
C  PRINT OUT RESULTS
        WRITE(6,12) Tout/(xkd*xkon),Y(1),Y(2),Y(3),Y(4),Y(5)
        OPEN(Unit=95,FILE='BP.DAT',STATUS='OLD')
        WRITE(95,22) Tout/(xkd*xkon),Y(1),Y(2),Y(3),Y(4),Y(5)
        tin=tout
 10   continue
 12   FORMAT( 14X,2HX=,G8.3,2X,5HY(1)=,D11.6,2X,5HY(2)=,D11.6,
     &        2X,5HY(3)=,E14.2,2X,5HY(4)=,D11.6,2X,5HY(5)=,D11.6)
 22   FORMAT( E14.6,E14.6,E14.6,E14.6,E14.6,E14.6)

        STOP
      END
C
C*********************  SUBROUTINE FCN
******************************
```

```
C
C     THIS SUBROUTINE CALCULATES THE DERIVATIVE OF EACH DEPENDENT
C  VARIABLE WITH RESPECT TO X, YPRIME(I).
C
C*****************************************************************
C
      SUBROUTINE FEX(N,X,Y,YPRIME)
      IMPLICIT REAL*8(A-H,O-Z)
      INTEGER N
      DIMENSION Y(5),YPRIME(5)
      common/class/b,rho,alpha,beta,gamma
      YPRIME(1)=(y(2)-y(3)*y(1))/(1.0d0+b*y(1))
      YPRIME(2)=(y(3)*y(1)-y(2))/(1.0d0+b*y(1))
      YPRIME(3)= ((-y(3)*rho*y(1) + rho*y(2))/(1.0d0+b*y(1)))-
                 (beta*Y(3)*gamma*Y(4))+(alpha*beta*Y(5)*gamma)
      YPRIME(4)=(-beta*Y(3)*Y(4))+(alpha*beta*Y(5))
      YPRIME(5)=(beta*Y(3)*Y(4))-(alpha*beta*Y(5))
      RETURN
      END
C
C****************************  SUBROUTINE FCNJ
*************************
C
C     THIS IS A DUMMY SUBROUTINE IF MF IS EQUAL TO 10/22 AND THE
C  JACOBIAN IS ESTIMATED NUMERICALLY.
C
C*****************************************************************
C
      SUBROUTINE JAC(N,X,Y,ML,MU,PD,NRPD)
      IMPLICIT REAL*8(A-H,O-Z)
      REAL*8 Y(5),PD(NRPD,5),X
      common/class/b,rho,alpha,beta,gamma
c
      pd(1,1) = ((-b*(y(2)-y(3)*y(1)))/((1.0d0+b*y(1))*
                (1.0d0+b*y(1))))-(y(3)/(1.0d0+b*y(1)))
      pd(1,2) = 1.0d0/(1.0d0+b*y(1))
      pd(1,3) = -y(1)/(1.0d0+b*y(1))
        pd(1,4) = 0
        pd(1,5) = 0
      pd(2,1) = ((b*(y(2)-y(3)*y(1)))/((1.0d0+b*y(1))*
                (1.0d0+b*y(1))))+(y(3)/(1.0d0+b*y(1)))
      pd(2,2) = -1.0d0/(1.0d0+b*y(1))
```

```
  pd(2,3) = y(1)/(1.0d0+b*y(1))
  pd(2,4) = 0
  pd(2,5) = 0
  pd(3,1) = ((rho*b*(y(3)*y(1)-y(2)))/((1.0d0+b*y(1))*
              (1.0d0+b*y(1))))-(y(3)*rho/(1.0d0+b*y(1)))
  pd(3,2) = rho/(1.0d0+b*y(1))
  pd(3,3) = (-rho*y(1)/(1.0d0+b*y(1)))
  pd(3,4) = -beta*Y(3)*gamma
  pd(3,5) = alpha*beta*gamma
  pd(4,1) = 0
  pd(4,2) = 0
  pd(4,3) = -beta*Y(4)
  pd(4,4) = -beta*Y(3)
  pd(4,5) = alpha*beta
  pd(5,1) = 0
  pd(5,2) = 0
  pd(5,3)     = beta*Y(4)
  pd(5,4) = beta*Y(3)
  pd(5,5) = -alpha*beta
RETURN
END
```

IGF-I/p9 HS BAE Cell System Model:

```
C
C**************************** ABSTRACT
*******************************
C
C    THIS PROGRAM APPLIES THE  LIBRARY ROUTINE LSODE TO THE
C  INTEGRATION ON A NON-STIFF SET OF ODE'S.  NOMENCLATURE FOR THIS
C  PROGRAM CAN BE FOUND IN FILE LSDP1.
C
C*****************************************************************
C  IGF-I/p9 HS BAE Cell System Model
c                     - Y(1) = u (dimensionless unbound receptors, R/Ro)
c                     - Y(2) = v (dimensionless bound receptors, C/Ro)
c                     - Y(3) = y (dimensionless ligand, Lo/Kd)
c                     - Y(4) = w (dimensionless unbound p9 HS, S/So)
c                     - Y(5) = z (dimensionless bound p9 HS, X/So)
c             p9 HS              pick Kons = 4 x 10+7 M-1s-1
c                                K_Ds = 1.5 x 10-8 M
c    initial conditions:                Y(1) = 1
c                                       Y(2) = 0
c                                       Y(3) = Lo/Kd
c                                       Y(4) = 1
c                                       Y(5) = 0
C    integrate from zero time (t=0) to 3 hours (t=10800 secs)
c
     IMPLICIT REAL*8(A-H,O-Z)
C    NONSTIFF PROBLEMS (MF = 10)
C    RWORK(20+16*NEQ), IWORK(20)
C    DIMENSION Y(5),ATOL(5),RWORK(100),IWORK(20)
C
C    STIFF PROBLEMS (MF=21(WITH JACOBIAN),22(WITHOUT JACOBIAN)
C    RWORK(22+9*NEQ+NEQ**2),IWORK(20+NEQ)
     DIMENSION Y(5), ATOL(5),RWORK(92),IWORK(22)
C
C    NONSTIFF PROBLEMS/STIFF (MF=22)
C    EXTERNAL FEX
C    STIFF PROBLEMS (MF=21)
     EXTERNAL FEX,JAC
C
     common/class/b,rho,alpha,beta,gamma
```

```
c  Parameter values
      Ro = 2.0d4
c      Ro=# receptors/cell
      xkd = .6d-9
c      Kd = koff/kon = affinity of ligand to receptor =M
      a = 5.0d-4
c      a = radius of a single cell
      D = 5.0d-7
c      D = diffusivity of ligand through binding buffer = cm2/s
      xkon = 4.0d7
c      kon = association rate constant for ligand and receptor = M-1s-1
      xLo = 5.7d-10
c      Lo = initial ligand concentration =M
      V=3.33d-5
c      V = binding buffer volume/avg. # of cells (15,000) = cm3
      So=1.4d-10
c      So = exogenous p9 HS added = M
      xkons=4.0d7
c      kons = association rate constant for ligand and p9 HS = M-1s-1
      xkds=1.5d-8
c      Kds = affinity of ligand to p9 HS = M
      xN = 6.023d23
c      N = Avogadro's # = #/mol
C     dimensionless groups
      b = xkon*Ro*1000/(4.0d0*3.1416d0*a*D*xN)
c      [(L/mol*s)*(#/cell)*(L/1000cm3)]/[(cm/cell)*(cm2/s)*(#/mol)]
      rho = (Ro*1000)/(V*xkd*xN)
c      [(#/cell)*(1000cm3/L)]/[(cm3*(mol/L)*(#/mol)]
      alpha =xkds/xkd
c      [M/M]
      beta = xkons/xkon
c      [(M-1s-1)/(M-1s-1)]
      gamma = So/xkd
c        [M/M]
      write(*,*) b,rho,alpha,beta,gamma
C  INITIAL CONDITIONS
      Y(1)=1.0d0
      Y(2)=0.0d0
      Y(3)=xlo/xkd
      Y(4)=1.0d0
      Y(5)=0.0d0
      Tin=0.0d0
```

```
      Tout =10.8d3
      Tin=tin*xkd*xkon
      Tout=Tout*xkd*xkon
      N = 100
      deltax =(tout-tin)/float(N)
C  DGEAR PARAMETER SPECIFICATIONS
      NEQ=5
      RTOL=1.E-6
      ITOL=1
      ATOL(1)=1.E-6
      ITASK=1
      ISTATE=1
      IOPT=0
C
c     nonstiff integrator
C      MF=10
C     LRW = 20*16*NEQ
C     LIW = 20
c     stiff integrator with jacobian
       MF = 21
       LRW = 22+9*NEQ+NEQ**2
       LIW = 20+NEQ
C  INTEGRATE IN EQUALLY SPACED SEGMENTS USING A DO-LOOP
       DO 10 K=1,N
         Tout=Tin+deltax
         CALL LSODE(FEX,NEQ,Y,Tin,Tout,ITOL,RTOL,ATOL,ITASK,ISTATE,IOPT,
     *               RWORK,LRW,IWORK,LIW,JAC,MF)
C  PRINT OUT RESULTS
         WRITE(6,12) Tout/(xkd*xkon),Y(1),Y(2),Y(3),Y(4),Y(5)
         OPEN(Unit=95,FILE='p9.DAT',STATUS='OLD')
         WRITE(95,22) Tout/(xkd*xkon),Y(1),Y(2),Y(3),Y(4),Y(5)
         tin=tout
 10    continue
 12    FORMAT( 14X,2HX=,G8.3,2X,5HY(1)=,D11.6,2X,5HY(2)=,D11.6,
     *             2X,5HY(3)=,E14.2,2X,5HY(4)=,D11.6,2X,5HY(5)=,D11.6)
 22    FORMAT( E14.6,E14.6,E14.6,E14.6,E14.6,E14.6)

         STOP
      END
C
C********************** SUBROUTINE FCN
******************************
```

```
C
C     THIS SUBROUTINE CALCULATES THE DERIVATIVE OF EACH DEPENDENT
C  VARIABLE WITH RESPECT TO X, YPRIME(I).
C
C*****************************************************************
C
      SUBROUTINE FEX(N,X,Y,YPRIME)
      IMPLICIT REAL*8(A-H,O-Z)
      INTEGER N
      DIMENSION Y(5),YPRIME(5)
      common/class/b,rho,alpha,beta,gamma
      YPRIME(1)=(y(2)-y(3)*y(1))/(1.0d0+b*y(1))
      YPRIME(2)=(y(3)*y(1)-y(2))/(1.0d0+b*y(1))
      YPRIME(3)= ((-y(3)*rho*y(1) + rho*y(2))/(1.0d0+b*y(1)))-
     &          (beta*Y(3)*gamma*Y(4))+(alpha*beta*Y(5)*gamma)
      YPRIME(4)=(-beta*Y(3)*Y(4))+(alpha*beta*Y(5))
      YPRIME(5)=(beta*Y(3)*Y(4))-(alpha*beta*Y(5))
      RETURN
      END
C
C***************************  SUBROUTINE FCNJ
**************************
C
C     THIS IS A DUMMY SUBROUTINE IF MF IS EQUAL TO 10/22 AND THE
C  JACOBIAN IS ESTIMATED NUMERICALLY.
C
C*****************************************************************
C
      SUBROUTINE JAC(N,X,Y,ML,MU,PD,NRPD)
      IMPLICIT REAL*8(A-H,O-Z)
      REAL*8 Y(5),PD(NRPD,5),X
      common/class/b,rho,alpha,beta,gamma
c
      pd(1,1) = ((-b*(y(2)-y(3)*y(1)))/((1.0d0+b*y(1))*
               (1.0d0+b*y(1))))-(y(3)/(1.0d0+b*y(1)))
      pd(1,2) = 1.0d0/(1.0d0+b*y(1))
      pd(1,3) = -y(1)/(1.0d0+b*y(1))
      pd(1,4) = 0
      pd(1,5) = 0
      pd(2,1) = ((b*(y(2)-y(3)*y(1)))/((1.0d0+b*y(1))*
               (1.0d0+b*y(1))))+(y(3)/(1.0d0+b*y(1)))
      pd(2,2) = -1.0d0/(1.0d0+b*y(1))
```

```
pd(2,3) = y(1)/(1.0d0+b*y(1))
pd(2,4) = 0
pd(2,5) = 0
pd(3,1) = ((rho*b*(y(3)*y(1)-y(2)))/((1.0d0+b*y(1))*
              (1.0d0+b*y(1))))-(y(3)*rho/(1.0d0+b*y(1)))
pd(3,2) = rho/(1.0d0+b*y(1))
pd(3,3) = (-rho*y(1)/(1.0d0+b*y(1)))
pd(3,4) = -beta*Y(3)*gamma
pd(3,5) = alpha*beta*gamma
pd(4,1) = 0
pd(4,2) = 0
pd(4,3) = -beta*Y(4)
pd(4,4) = -beta*Y(3)
pd(4,5) = alpha*beta
pd(5,1) = 0
pd(5,2) = 0
pd(5,3) = beta*Y(4)
pd(5,4) = beta*Y(3)
pd(5,5) = -alpha*beta
RETURN
END
```

Complex BAE Cell System Model:

```
C
C****************************  ABSTRACT
*********************************
C
C    THIS PROGRAM APPLIES THE  LIBRARY ROUTINE LSODE TO THE
C  INTEGRATION ON A NON-STIFF SET OF ODE'S.  NOMENCLATURE FOR THIS
C  PROGRAM CAN BE FOUND IN FILE LSDP1.
C
C*********************************************************************
C IGFBP and p9 HS Complex BAE Cell
c                    - Y(1) = u (dimensionless unbound receptors, R/Ro)
c                    - Y(2) = v (dimensionless bound receptors, C/Ro)
c                    - Y(3) = y (dimensionless ligand, Lo/Kd)
c                    - Y(4) = w (dimensionless unbound IGFBP-3, S/So)
c                    - Y(5) = z (dimensionless bound IGFBP-3, X/So)
c                    - Y(6) = p (dimensionless unbound p9 HS, P/Po)
c                    - Y(7) = q (dimensionless bound p9 HS, Q/Po)
c             IGFBP-3                   pick Kons = 4 x 10+7 M-1s-1
c             p9 HS                     pick konp = 4 x 10+7 M-1s-1
c                                       K_D^s = 3 x 10-9 M
c                                       K_D^p = 1.5 x 10-8 M
c    initial conditions:                Y(1) = 1
c                                       Y(2) = 0
c                                       Y(3) = Lo/Kd
c                                       Y(4) = 1
c                                       Y(5) = 0
c                                       Y(6) = 1
C                                       Y(7) = 0
C    integrate from zero time (t=0) to 3 hours (t=10800 secs)
c
     IMPLICIT REAL*8(A-H,O-Z)
C    NONSTIFF PROBLEMS (MF = 10)
C    RWORK(20+16*NEQ), IWORK(20)
C    DIMENSION Y(7),ATOL(7),RWORK(132),IWORK(27)
C
C    STIFF PROBLEMS (MF=21(WITH JACOBIAN),22(WITHOUT JACOBIAN)
C    RWORK(22+9*NEQ+NEQ**2),IWORK(20+NEQ)
     DIMENSION Y(7), ATOL(7),RWORK(135),IWORK(27)
```

```
C
C   NONSTIFF PROBLEMS/STIFF (MF=22)
C   EXTERNAL FEX
C   STIFF PROBLEMS (MF=21)
    EXTERNAL FEX,JAC
C
    common/class/b,rho,alpha,beta,gamma,sigma,xkappa,phi
c Parameter values
    Ro = 2.0d4
c     Ro=# receptors/cell
    xkd = .6d-9
c     Kd = koff/kon = affinity of ligand to receptor =M
    a = 5.0d-4
c     a = radius of a single cell
    D = 5.0d-7
c     D = diffusivity of ligand through binding buffer = cm2/s
    xkon =4d7
c     kon = association rate constant for ligand and receptor = M-1s-1
    xLo = 5.7d-10
c     Lo = initial ligand concentration =M
    V=3.33d-5
c     V = binding buffer volume/avg. # of cells (15,000) = cm3
    So=2.8d-9
c     So = exogenous IGFBP-3 added = M
    Po=1.4d-10
c       Po = exogenous p9 HS added = M
    xkons=4.0d7
c     kons = association rate constant for ligand and IGFBP-3 = M-1s-1
    xkonp=4.0d7
c       konp = association rate constant for ligand and p9 HS = M-1s-1
    xkds=3.0d-9
c     Kds = affinity of ligand to IGFBP-3 = M
    xkdp=1.5d-8
c       Kdp = affinity of ligand to p9 HS = M
    xN = 6.023d23
c     N = Avogadro's # = #/mol
C    dimensionless groups
    b = xkon*Ro*1000/(4.0d0*3.1416d0*a*D*xN)
c     [(L/mol*s)*(#/cell)*(L/1000cm3)]/[(cm/cell)*(cm2/s)*(#/mol)]
    rho = (Ro*1000)/(V*xkd*xN)
c     [(#/cell)*(1000cm3/L)]/[(cm3*(mol/L)*(#/mol)]
    alpha =xkds/xkd
```

```
c     [M/M]
      sigma =xkdp/xkd
c        [M/M]
      beta = xkons/xkon
c     [(M-1s-1)/(M-1s-1)]
      xkappa = xkonp/xkon
c        [(M-1s-1)/(M-1s-1)]
      gamma = So/xkd
c        [M/M]
      phi  = Po/xkd
c        [M/M]
      write(*,*) b,rho,alpha,beta,gamma,sigma,xkappa,phi
C  INITIAL CONDITIONS
      Y(1)=1.0d0
      Y(2)=0.0d0
      Y(3)=xlo/xkd
      Y(4)=1.0d0
      Y(5)=0.0d0
      Y(6) = 1.0d0
      Y(7) = 0.0d0
      Tin=0.0d0
      Tout =5d0
      Tin=tin*xkd*xkon
      Tout=Tout*xkd*xkon
      N = 100
      deltax =(tout-tin)/float(N)
C  DGEAR PARAMETER SPECIFICATIONS
      NEQ=7
      RTOL=1.E-6
      ITOL=1
      ATOL(1)=1.E-6
      ITASK=1
      ISTATE=1
      IOPT=0
C
c     nonstiff integrator
C      MF=10
C      LRW = 20*16*NEQ
C      LIW = 20
c     stiff integrator with jacobian
       MF = 21
       LRW = 22+9*NEQ+NEQ**2
```

```
      LIW = 20+NEQ
C  INTEGRATE IN EQUALLY SPACED SEGMENTS USING A DO-LOOP
      DO 10 K=1,N
        Tout=Tin+deltax
        CALL LSODE(FEX,NEQ,Y,Tin,Tout,ITOL,RTOL,ATOL,ITASK,ISTATE,IOPT,
     +             RWORK,LRW,IWORK,LIW,JAC,MF)
C  PRINT OUT RESULTS
        WRITE(6,12) Tout/(xkd*xkon),Y(1),Y(2),Y(3),Y(4),Y(5),Y(6),Y(7)
        OPEN(Unit=95,FILE='COMBO.DAT',STATUS='OLD')
        WRITE(95,22) Tout/(xkd*xkon),Y(1),Y(2),Y(3),Y(4),Y(5),Y(6),Y(7)
        tin=tout
 10   continue
 12   FORMAT( 14X,2HX=,G8.3,2X,5HY(1)=,D11.6,2X,5HY(2)=,D11.6,
     +        2X,5HY(3)=,E14.2,2X,5HY(4)=,D11.6,2X,5HY(5)=,D11.6,
     +        2X,5HY(6)=,D11.6,2X,5HY(7)=,D11.6)
 22   FORMAT( E14.6,E14.6,E14.6,E14.6,E14.6,E14.6,E14.6,E14.6)

        STOP
      END
C
C********************* SUBROUTINE FCN
******************************
C
C    THIS SUBROUTINE CALCULATES THE DERIVATIVE OF EACH DEPENDENT
C  VARIABLE WITH RESPECT TO X, YPRIME(I).
C
C*****************************************************************
C
      SUBROUTINE FEX(N,X,Y,YPRIME)
      IMPLICIT REAL*8(A-H,O-Z)
      INTEGER N
      DIMENSION Y(7),YPRIME(7)
      common/class/b,rho,alpha,beta,gamma,sigma,xkappa,phi
      YPRIME(1)=(y(2)-y(3)*y(1))/(1.0d0+b*y(1))
      YPRIME(2)=(y(3)*y(1)-y(2))/(1.0d0+b*y(1))
      YPRIME(3)= ((-y(3)*rho*y(1) + rho*y(2))/(1.0d0+b*y(1)))-
     +            (beta*Y(3)*gamma*Y(4))+(alpha*beta*Y(5)*gamma)
     +           -(xkappa*Y(3)*phi*Y(6))+(sigma*xkappa*Y(7)*phi)
      YPRIME(4)=(-beta*Y(3)*Y(4))+(alpha*beta*Y(5))
      YPRIME(5)=(beta*Y(3)*Y(4))-(alpha*beta*Y(5))
      YPRIME(6)=(-xkappa*Y(3)*Y(6))+(sigma*xkappa*Y(7))
      YPRIME(7)=(xkappa*Y(3)*Y(6))-(sigma*xkappa*Y(7))
```

```
      RETURN
      END
C
C*****************************  SUBROUTINE FCNJ
************************
C
C     THIS IS A DUMMY SUBROUTINE IF MF IS EQUAL TO 10/22 AND THE
C   JACOBIAN IS ESTIMATED NUMERICALLY.
C
C*********************************************************************
C
      SUBROUTINE JAC(N,X,Y,ML,MU,PD,NRPD)
      IMPLICIT REAL*8(A-H,O-Z)
      REAL*8 Y(7),PD(NRPD,7),X
      common/class/b,rho,alpha,beta,gamma,sigma,xkappa,phi
c
      pd(1,1) = ((-b*(y(2)-y(3)*y(1)))/((1.0d0+b*y(1))*
                (1.0d0+b*y(1))))-(y(3)/(1.0d0+b*y(1)))
      pd(1,2) = 1.0d0/(1.0d0+b*y(1))
      pd(1,3) = -y(1)/(1.0d0+b*y(1))
      pd(1,4) = 0
      pd(1,5)= 0
      pd(1,6) = 0
      pd(1,7) = 0
      pd(2,1) = ((b*(y(2)-y(3)*y(1)))/((1.0d0+b*y(1))*
                (1.0d0+b*y(1))))+(y(3)/(1.0d0+b*y(1)))
      pd(2,2) = -1.0d0/(1.0d0+b*y(1))
      pd(2,3) = y(1)/(1.0d0+b*y(1))
      pd(2,4) = 0
      pd(2,5) = 0
      pd(2,6) = 0
      pd(2,7) = 0
      pd(3,1) = ((rho*b*(y(3)*y(1)-y(2)))/((1.0d0+b*y(1))*
                (1.0d0+b*y(1))))-(y(3)*rho/(1.0d0+b*y(1)))
      pd(3,2) = rho/(1.0d0+b*y(1))
      pd(3,3) = (-rho*y(1)/(1.0d0+b*y(1)))
      pd(3,4) = -beta*Y(3)*gamma
      pd(3,5) = alpha*beta*gamma
      pd(3,6) = -xkappa*Y(3)*phi
      pd(3,7) = sigma*xkappa*phi
```

```
  pd(4,1) = 0
  pd(4,2) = 0
  pd(4,3) = -beta*Y(4)
  pd(4,4) = -beta*Y(3)
  pd(4,5) = alpha*beta
  pd(4,6) = 0
  pd(4,7) = 0
  pd(5,1) = 0
  pd(5,2) = 0
  pd(5,3)      = beta*Y(4)
  pd(5,4) = beta*Y(3)
  pd(5,5) = -alpha*beta
  pd(5,6) = 0
  pd(5,7) = 0
  pd(6,1) = 0
  pd(6,2) = 0
  pd(6,3) = -xkappa*Y(6)
  pd(6,4) = 0
  pd(6,5) = 0
  pd(6,6) = -xkappa*Y(3)
  pd(6,7) = sigma*xkappa
  pd(7,1) = 0
  pd(7,2) = 0
  pd(7,3) = xkappa*Y(4)
  pd(7,4) = 0
  pd(7,5) = 0
  pd(7,6) = xkappa*Y(3)
  pd(7,7) = -sigma*xkappa
RETURN
END
```

CURRICULUM VITAE

EDUCATION:	Virginia Polytechnic Institute and State University Master of Science, Chemical Engineering, May 1997
	University Of Mississippi Bachelor of Science, Chemical Engineering, May 1995
RESEARCH EXPERIENCE:	Dr. Kim Forsten's Lab, VA Tech January 1996 - May 1997
TEACHING EXPERIENCE:	Unit Operations Lab, VA Tech May 1996 - June 1996
	Mass and Energy Balances, VA Tech Teaching Assistant, Fall 1995, 1996
	Process Modeling, VA Tech Teaching Assistant, Spring 1996
	Heat Transfer, VA Tech Teaching Assistant, Spring 1997
HONORS / ACTIVITIES:	Graduate Student Advisory Delegate, VA Tech College of Engineering Graduate Student Committee, VA Tech National Merit Scholar Chancellor's and Dean's Honor Roll Who's Who Among National College Students ASB Cabinet - Director of Student Development Sorority Treasurer ASB Committee(s) Chairman: *Health Advisory,* *Student Wellness,* *Environmental Awareness* Student Alumni Council American Institute of Chemical Engineers - Treasurer Society of Women Engineers - Secretary / Treasurer Phi Eta Sigma - Academic Honorary Alpha Lambda Delta - Academic Honorary

Student Programming Board
Order of Omega
Intramural Sports - softball, football, volleyball
Ole Miss Sexual Harassment Hearing Panel
Three Time Miss Majorette of Virginia
Four Time Virginia State Solo Twirling Champion
Three Time Virginia State Strutting Champion
Second Place, World Solo Twirling Championships
Second Place, World Strutting Championships
Fifth Place, Miss Majorette of America