LIST OF REFERENCES


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:

\[ y_p(x) = aC_1 + C_2, \]

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.

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

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:

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

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

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.

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:

\[
\frac{dB}{dt} = k_{on}^s[I][BP] - k_{off}^s[B],
\]

(5)

where \( I = I_0 - B \), \( BP = BP_0 - B \). At steady state the rate of change of the IGF-I/IGFBP-3 complex (B) is zero and Equation 5 becomes:

\[
I_0 = K_D^s[B]/[BP_0 - B] + [B],
\]

(6)

where \( K_D^s = \frac{k_{off}^s}{k_{on}^s} \). Equation 6 becomes \( y \) “predicted” (Equation 1) with \( I_0 = y_p, K_D = a, B/[BP_0 - B] = C_1 \) and \( [B] = C_2 \). Least squares analysis from experimental assay data yielded \( K_D \) values of \( 6.2 \times 10^{-9} \) M for the biodot assay and \( 3 \times 10^{-9} \) 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:

\[
\frac{dP}{dt} = k_{on}^p[I][PG] - k_{off}^p[P],
\]

(7)

where \( I = I_0 - P \), \( PG = PG_0 - P \). At steady state the rate of change of IGF-I/p9 HS complex (P) is zero and Equation 7 becomes:

\[
I_0 = K_D^p[P]/[PG_0 - P] + [P],
\]

(8)

where \( K_D^p = \frac{k_{off}^p}{k_{on}^p} \). Equation 8 becomes \( y \) “predicted” (Equation 1) with \( I_0 = y_p, K_D = a, P/[PG_0 - P] = C_1 \) and \( [P] = C_2 \). Least squares analysis from experimental assay data yielded \( K_D \) values of \( 2.2 \times 10^{-7} \) M for the biodot assay and \( 1.5 \times 10^{-8} \) M for the charcoal assay.
Basic BAE Cell System Model:

C
C**************************************************************************
C
ABSTRACT
**************************************************************************
C
C     THIS PROGRAM APPLIES THE LIBRARY ROUTINE LSODE TO THE INTEGRATION ON A NON-STIFF SET OF ODE’S. NOMENCLATURE FOR THIS PROGRAM CAN BE FOUND IN FILE LSDP1.
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
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
NONSTIFF PROBLEMS/STIFF (MF = 22)
C EXTERNAL FEX
C STIFF PROBLEMS (MF = 21)
  EXTERNAL FEX,J AC
C
common/class/b,rho
C Parameter values
C 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  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
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, I TOL, RTOL, ATOL, I TASK, I STATE, I OPT,
               1RWORK, LRW, I WORK, LIW, J AC, 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)
C STOP
C END
C******************************** SUBROUTINE FCN
C***************************************************************************
C THIS SUBROUTINE CALCULES THE DERIVATIVE OF EACH DEPENDENT
C VARIABLE WITH RESPECT TO X, YPRIME(I).
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 JAC(N,X,Y,ML,MU,PD,NRPD)
C    IMPLICIT REAL*8(A-H,O-Z)
C    REAL*8 Y(3),PD(NRPD,3),X
C    common/class/b,rho
C
C    pd(1,1) = ((-b*(y(2)-y(3)*y(1)))/((1.0d0+b*y(1))*(1.0d0+b*y(1))))-
C             (y(3)/(1.0d0+b*y(1)))
C    pd(1,2) = 1.0d0/(1.0d0+b*y(1))
C    pd(1,3) = -y(1)/(1.0d0+b*y(1))
C    pd(2,1) = ((b*(y(2)-y(3)*y(1)))/
C             ((1.0d0+b*y(1))*(1.0d0+b*y(1))))+(y(3)/(1.0d0+b*y(1)))
C    pd(2,2) = -1.0d0/(1.0d0+b*y(1))
C    pd(2,3) = y(1)/(1.0d0+b*y(1))
C    pd(3,1) = ((rho*b*(y(3)*y(1)-y(2)))/
C             ((1.0d0+b*y(1))*(1.0d0+b*y(1))))-(y(3)*rho/
C             (1.0d0+b*y(1)))
C    pd(3,2) = rho/(1.0d0+b*y(1))
C    pd(3,3) = (-rho*y(1)/(1.0d0+b*y(1)))
C    RETURN
C    END
IGF-I/IGFBP-3 BAE Cell System Model:

C
C*************************************************************************** ABSTRACT
***************************************************************************
C
C THIS PROGRAM APPLIES THE LIBRARY ROUTINE LSODE TO THE INTEGRATION ON A NON-STIFF SET OF ODE'S. NOMENCLATURE FOR THIS PROGRAM CAN BE FOUND IN FILE LSDP1.
C
C***************************************************************************
C IGF-I/IGFBP-3 BAE Cell System Model
C
C - Y(1) = u (dimensionless unbound receptors, R/Ro)
C - Y(2) = v (dimensionless bound receptors, C/Ro)
C - Y(3) = y (dimensionless ligand, L/Lo)
C - Y(4) = w (dimensionless unbound IGFBP-3, S/So)
C - Y(5) = z (dimensionless bound IGFBP-3, X/So)
C
C IGF-I/IGFBP-3 pick Kons = 4 x 10^7 M^-1s^-1
C K_D = 3 x 10^-9 M
C
C initial conditions: Y(1) = 1
C Y(2) = 0
C Y(3) = L/Lo
C Y(4) = 1
C Y(5) = 0
C
C integrate from zero time (t=0) to 3 hours (t=10800 secs)
C
C IMPLICIT REAL*8(A-H,O-Z)
C NONSTIFF PROBLEMS (M_F = 10)
C RWORK(20+16*NEQ), IWORK(20)
C DIMENSION Y(5), ATOL(5), RWORK(100), IWORK(20)
C
C STIFF PROBLEMS (M_F=21(WITH JACOBIAN),22(WITHOUT JACOBIAN)
C RWORK(22+9*NEQ+NEQ**2), IWORK(20+NEQ)
C DIMENSION Y(5), ATOL(5), RWORK(92), IWORK(22)
C
C NONSTIFF PROBLEMS/STIFF (M_F=22)
C EXTERNAL FEX
C STIFF PROBLEMS (M_F=21)
C EXTERNAL FEX,J AC
C
common/class/b,rho,alpha,beta, gamma
c Parameter values
Ro = 2.0d4
Ro=# receptors/cell
xkd = .6d-9
Kd = koff/kon = affinity of ligand to receptor =M
a = 5.0d-4
a = radius of a single cell
D = 5.0d-7
D = diffusivity of ligand through binding buffer = cm2/ s
xkon = 4.0d7
kon = association rate constant for ligand and receptor = M-1s-1
xLo = 5.7d-10
Lo = initial ligand concentration = M
V = 3.33d-5
V = binding buffer volume/ avg. # of cells (15,000) = cm3
So = 2.8d-9
So = exogenous IGFBP-3 added = M
xkons = 4.0d7
kons = association rate constant for ligand and IGFBP-3 = M-1s-1
xkds = 3d-9
Kds = affinity of ligand to IGFBP-3 = M
xN = 6.023d23
N = Avogadro’s # =#/mol
C dimensionless groups
b = xkon*Ro*1000/(4.0d0*3.1416d0*a*D*xN)
[(L/mol*s)*(#/cell)*(L/1000cm3)]/[(cm/cell)*(cm2/s)*(#/mol)]
rho = (Ro*1000)/(V*xkd*xN)
[(#/cell)*(1000cm3/L)]/[(cm3*(mol/L)*(#/mol)]
alpha = xkds/xkd
[M/M]
beta = xkons/xkon
[(M-1s-1)/(M-1s-1)]
gamma = So/xkd
[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
   I STATE=1
   IOPT=0
C         nonstiff integrator
   MF=10
   LRW = 20*16*NEQ
   LI W = 20
C         stiff integrator with jacobian
   MF = 21
   LRW = 22 +9*NEQ+NEQ**2
   LI W = 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,I STATE,IOPT,
             RWORK,LRW,I WORK,LI W,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
********************************************************************
THIS SUBROUTINE CALCULATES THE DERIVATIVE OF EACH DEPENDENT VARIABLE WITH RESPECT TO X, YPRIME(I).

**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))-
       (B*Y(3)*GAMMA*Y(4)+(ALPHA*BETA*Y(5)*GAMMA))-
       (B*Y(3)*Y(4))+(ALPHA*BETA*Y(5))-
       (B*Y(3)*Y(4))-(ALPHA*BETA*Y(5))
RETURN
END

**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

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:

THIS PROGRAM APPLIES THE LIBRARY ROUTINE LSODE TO THE INTEGRATION ON A NON-STIFF SET OF ODE'S. NOMENCLATURE FOR THIS PROGRAM CAN BE FOUND IN FILE LSDP1.

IGF-I/p9 HS BAE Cell System Model

- \( Y(1) = u \) (dimensionless unbound receptors, \( R/R_0 \))
- \( Y(2) = v \) (dimensionless bound receptors, \( C/R_0 \))
- \( Y(3) = y \) (dimensionless ligand, \( L_0/K_d \))
- \( Y(4) = w \) (dimensionless unbound p9 HS, \( S/S_0 \))
- \( Y(5) = z \) (dimensionless bound p9 HS, \( X/S_0 \))

p9 HS pick \( K_{ons} = 4 \times 10^7 \text{ M}^{-1}\text{s}^{-1} \)
\( K_d = 1.5 \times 10^{-8} \text{ M} \)

initial conditions: \( Y(1) = 1 \)
\( Y(2) = 0 \)
\( Y(3) = L_0/K_d \)
\( Y(4) = 1 \)
\( Y(5) = 0 \)

integrate from zero time (\( t=0 \)) to 3 hours (\( t=10800 \text{ secs} \))

IMPLICIT REAL*8(A-H,O-Z)
NONSTIFF PROBLEMS (\( MF = 10 \))
RWORK(20+16*NEQ), IWORK(20)
DIMENSION Y(5), ATOL(5), RWORK(100), IWORK(20)

STIFF PROBLEMS (\( MF=21 \) (WITH JACOBIAN), \( 22 \) (WITHOUT JACOBIAN))
RWORK(22+9*NEQ+NEQ**2), IWORK(20+NEQ)
DIMENSION Y(5), ATOL(5), RWORK(92), IWORK(22)

NONSTIFF PROBLEMS/STIFF (\( MF=22 \))
EXTERNAL FEX
STIFF PROBLEMS (\( MF=21 \))
EXTERNAL FEX, JAC

common/ class/ b,rho,alpha,beta,gamma
c Parameter values
    Ro = 2.0d4
    Ro=# receptors/cell
    xkd = .6d-9
    Kd = koff/kon = affinity of ligand to receptor =M
    a = 5.0d-4
    a = radius of a single cell
    D = 5.0d-7
    D = diffusivity of ligand through binding buffer = cm2/s
    xkon = 4.0d7
    kon = association rate constant for ligand and receptor = M-1s-1
    xLo = 5.7d-10
    Lo = initial ligand concentration =M
    V = 3.33d-5
    V = binding buffer volume/avg. # of cells (15,000) = cm3
    So = 1.4d-10
    So = exogenous p9 HS added = M
    xkons = 4.0d7
    kons = association rate constant for ligand and p9 HS =M-1s-1
    xkds = 1.5d-8
    Kds = affinity of ligand to p9 HS = M
    xN = 6.023d23
    N = Avogadro’s # =#/mol
C dimensionless groups
    b = xkon*Ro*1000/(4.0d0*3.1416d0*a*D*xN)
    rho = (Ro*1000)/(V*xkd*xN)
    [(L/mol*s)*(#/cell)/(L/1000cm3)]/[cm2/s*(#/mol)]
    alpha = xkds/xkd
    [(#/cell)*(1000cm3/L)]/[cm3*(mol/L)*(#/mol)]
    beta = xkons/xkon
    [(M-1s-1)/(M-1s-1)]
    gamma = So/xkd
    [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 DGGEAR PARAMETER SPECIFICATIONS
NEQ = 5
RTOL = 1.E-6
ITOL = 1
ATOL(1) = 1.E-6
ITASK = 1
ISTATE = 1
IOPT = 0

C nonstiff integrator
MF = 10
LRW = 20 * 16 * NEQ
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, I STATE, I OPT,
             RWORK, LRW, I WORK, LI W, 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*****************************************************************************
SUBROUTINE FCN
*****************************************************************************
THIS SUBROUTINE CALCULATES THE DERIVATIVE OF EACH DEPENDENT VARIABLE WITH RESPECT TO X, YPRIME(I).

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

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:
C 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)
C DIMENSION Y(7), ATOL(7), RWORK(135), IWORK(27)
C NONSTIFF PROBLEMS/STIFF (MF=22)
C EXTERNAL FEX
C STIFF PROBLEMS (MF=21)
C EXTERNAL FEX,JAC

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

beta = xkons/xkon
\[ \text{[M/M]} \]

xkappa = xkonp/xkon
\[ \text{[(M-1s-1)/(M-1s-1)]} \]

gamma = So/xkd
\[ \text{[M/M]} \]

phi = Po/xkd
\[ \text{[M/M]} \]

write(*,*) b,rho,alpha,beta,gamma,sigma,xkappa,phi

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 = 5.0d0
Tin = tin * xkd * xkon
Tout = Tout * xkd * xkon
N = 100
deltax = (tout - tin) / float(N)

DGEAR PARAMETER SPECIFICATIONS
NEQ = 7
RTOL = 1.E-6
ITOL = 1
ATOL(1) = 1.E-6
ITASK = 1
ISTATE = 1
IOPT = 0

nonstiff integrator
MF = 10
LRW = 20*16*NEQ
LIW = 20

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, I TOL, RTOL, ATOL, I TASK, I STATE, I OPT,
             RWORK, LRW, I WORK, 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 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 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)/((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
\begin{align*}
\text{pd}(4,1) &= 0 \\
\text{pd}(4,2) &= 0 \\
\text{pd}(4,3) &= -\beta Y(4) \\
\text{pd}(4,4) &= -\beta Y(3) \\
\text{pd}(4,5) &= \alpha \beta \\
\text{pd}(4,6) &= 0 \\
\text{pd}(4,7) &= 0 \\
\text{pd}(5,1) &= 0 \\
\text{pd}(5,2) &= 0 \\
\text{pd}(5,3) &= \beta Y(4) \\
\text{pd}(5,4) &= \beta Y(3) \\
\text{pd}(5,5) &= -\alpha \beta \\
\text{pd}(5,6) &= 0 \\
\text{pd}(5,7) &= 0 \\
\text{pd}(6,1) &= 0 \\
\text{pd}(6,2) &= 0 \\
\text{pd}(6,3) &= -x\kappa Y(6) \\
\text{pd}(6,4) &= 0 \\
\text{pd}(6,5) &= 0 \\
\text{pd}(6,6) &= -x\kappa Y(3) \\
\text{pd}(6,7) &= \sigma x\kappa \\
\text{pd}(7,1) &= 0 \\
\text{pd}(7,2) &= 0 \\
\text{pd}(7,3) &= x\kappa Y(4) \\
\text{pd}(7,4) &= 0 \\
\text{pd}(7,5) &= 0 \\
\text{pd}(7,6) &= x\kappa Y(3) \\
\text{pd}(7,7) &= -\sigma x\kappa \\
\text{RETURN} \\
\text{END}
\end{align*}
CURRICULUM VITAE

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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