Supplemental Material for "Identifying Determinants of EGFR-Targeted Therapeutic Biochemical Efficacy Using Computational Modeling," Calixte S. Monast and Matthew J. Lazzara

Supplemental Figure Legends

Figure S1: Local sensitivity analysis to identify determinants of t_{50} values for 50 nM gefitinib and cetuximab. Sensitivity of t_{50} values to perturbations of 10-fold in each of the model parameters was computed for (A) gefitinib or (B) cetuximab. Sensitivities were reported as the absolute value of the difference in the logarithm of the base t_{50} and the perturbed t_{50} values and then normalized to the maximum. This analysis was performed for 1.6 nM EGF, 1.6 nM AR, and 160 nM AR and 50 nM therapeutic.

Figure S2: Local sensitivity analyses to identify determinants of IC_{50} and t_{50} values calculated for the effect of gefitinib and cetuximab on EGFR-GRB2 association. Sensitivity of IC_{50} (A and B) or t_{50} (C and D) values for EGFR-GRB2 association (instead of EGFR phosphorylation) to perturbations of 10-fold in each of the model parameters was computed for (A and C) gefitinib or (B and D) cetuximab. Sensitivities were reported as the absolute value of the difference in the logarithm of the base IC_{50} or t_{50} and the perturbed values and then normalized to the maximum. This analysis was performed for 1.6 nM EGF, 1.6 nM AR, and 160 nM AR and 1 μM therapeutic.

Figure S3: Comparison of previously published experimental data used to train the model and best-fit model results. To determine dephosphorylation parameters the model (lines) was fit to previously published experimental data (filled circles)[1] for the effects of: (A) 1 or 10 ng/mL EGF or 100 μM of the phosphatase inhibitor pervanadate (PV); or (B and C) 4 μM gefitinib on

EGFR phosphorylation (pEGFR). For (A), times indicate incubation times for each compound. For panels (B) and (C), times indicate incubation times of gefitinib after a 4 min incubation with the indicated concentration of EGF. Measurements were made in parental HeLa cells (A and B) or HeLa cells with impaired EGFR internalization through expression of the K44A dynamin mutant (C). Data from K44A HeLa cells were included to help constrain the rate of EGFR dephosphorylation at the cell surface. Percentages of phosphorylated EGFR were measured using an immunoprecipitation approach described in detail in our previous study.[1]

References for figure legends

1. Monast CS, Furcht CM, Lazzara MJ. Computational analysis of the regulation of EGFR by protein tyrosine phosphatases. *Biophys J* 2012, **102**(9)**:** 2012-2021.

Description of Model Framework

Model Reactions

For each type of reaction, the following information is provided:

1. Compartment in which the reaction occurs;
2. Example reaction;
3. Description of the various species that participate in the reaction (unless otherwise noted, this description does not depend upon which compartment the receptor is in).

key:

R = EGF receptor monomer
L= ligand (EGF or AR)
A = ATP
(LR) = ligand-receptor complex
(LAR) = ligand- and ATP-bound receptor complex
(AR) = ATP-bound receptor
Xp = phosphorylated receptor species X (could be R, LR, LAR)
G2 = GRB2 adapter
(G2Rp) = GRB2-phosphorylated receptor complex
T_{gef} = therapeutic (gefitinib)
T_{cet} = therapeutic (cetuximab)
(T_xR) = therapeutic x-receptor complex
[(X)(Y)] = species X and Y in a dimer complex
X_s or $(X)_s$ = species or complex X present in the cell surface compartment
X_i or $(X)_i$ = species or complex X present in the cell interior compartment
forward reactions are indicated by "→"
reversible reactions are indicated by "↔"

Ligand binding

Example reaction: L + R ↔ (LR)
Compartments: surface and cell interior
Parameters: $k_{L,fs}$, $k_{L,rs}$, $k_{L,fi}$, $k_{L,ri}$
Relevant species: Ligand binds receptor monomers and dimers that are not ligand- or cetuximab-bound.

Cetuximab binding

Example: T_{cet} + R ↔ (T_{cet}R)
Compartments: surface
Parameters: $k_{c,f}$, $k_{c,r}$
Rules: In the cell surface compartment, cetuximab binds receptor monomer species that are not ligand- or cetuximab-bound.

ATP binding

Example: A + R ↔ (AR)
Compartments: surface and interior

Parameters: $k_{A,f}$, $k_{A,r}$
Rules: ATP binds receptors that are not ATP- or gefitinib-bound.

Gefitinib binding
Example: T_{gef} + R ↔ (T_{gef}R)
Compartments: surface and interior
Parameters: $k_{g,f}$, $k_{g,r}$
Rules: Gefitinib binds receptor species that are not ATP-bound or gefitinib-bound.

Dimerization
Example: (LR) + (LR) ↔ [(LR)(LR)]
Compartments: surface and interior
Parameters: $k_{d,rL}$, $k_{d,r}$, $k_{d,fs}$, $k_{d,fi}$
Rules: Dimerization occurs between identical receptor monomers. For example, two monomers bound with ATP are permitted to dimerize, but a monomer bound with ATP and a monomer bound with gefitinib may not dimerize. As mentioned in the main text, this symmetry requirement for dimerization was not enforced with respect to receptor ligand occupancy status due to specific experimental evidence for the formation of dimers bound with only a single ligand molecule (see additional discussion in *Methods*).

Phosphorylation
Example: [(LAR)(LAR)] → [(LRp)(LRp)]
Compartments: surface and interior
Parameters: k_p , $k_{p,L}$
Rules: Phosphorylation occurs within receptor dimers bound with ATP that are not already phosphorylated. ATP bound to receptor dimers is consumed by this reaction.
Dephosphorylation
Example: (LRp) → (LR)
Compartments: surface and interior
Parameters: $k_{dp,s}$, $k_{dp,i}$
Rules: Dephosphorylation occurs for receptor species that are phosphorylated and not bound by GRB2. This process occurs at different rates depending on whether the receptor species is localized to the cell surface or the cell interior.

GRB2 binding
Example: G2 + Rp ↔ (G2Rp)
Compartments: surface and interior
Parameters: $k_{G2,f}$, $k_{G2,r}$
Rules: GRB2 binds phosphorylated receptor species.

Internalization

Example: $(G2Rp)_s \rightarrow (G2Rp)_i$
Compartments: from surface to interior
Parameters: k_i
Rules: Receptor species in the cell surface compartment bound by GRB2 are permitted to irreversibly internalize (translocate to the cell interior compartment).

Receptor recycling
Example: $R_i \rightarrow R_s$
Compartments: from interior to surface
Parameters: k_x , f_{rE} , f_r
Rules: All receptor species within the cell interior compartment recycle. Ligand-bound receptors recycle at a slower rate compared to receptors not bound by ligand.

Receptor degradation
Example: $R_i \rightarrow 0$
Compartments: interior only
Parameters: k_x , $(1-f_{rE})$, $(1-f_r)$
Rules: All receptor species within the cell interior compartment degrade. Ligand-bound receptors degrade at a faster rate compared to receptors not bound by ligand.

Example Model Code

MATLAB functions necessary to simulate a simple EGF timecourse using our model framework:

```
function [] = main()

%constants
targetEGFR = 50000; %Berkers et al., 1991
targetKe = 0.13; %MJL HeLa.WT
keEGFconc = 0.00156; %10 ng/mL

kadptonREF = 16; %1/uM/s (majority constant, Morimatsu et al., 2007)
AvNum = 6.0221415e23; %#/mol
um3toL = 1e-15; %cubic micro to liter conversion
micro = 1e-6;
Rcell = 10; %microns
Vcell = 4/3*pi*Rcell^3; %cubic microns
newVcell = Vcell*um3toL; %liters
kadpton = kadptonREF*60/newVcell/AvNum/micro; %#/cell
kadptoff = 7.6*60; %1/s (majority constant, Morimatsu et al., 2007)

Grb2REF = 0.085; %uM (Kholodenko et al., 1999)
adpt = Grb2REF*newVcell*micro*AvNum;

KDdimerREF = 6; %uM (Shan et al., Cell, 2012)
KDdimer = KDdimerREF*newVcell*micro*AvNum;

%parameter names
paramNames{1} = 'kegfon';
paramNames{2} = 'kegfoff';
paramNames{3} = 'kegfonint';
paramNames{4} = 'kegfoffint';
paramNames{5} = 'katpon';
paramNames{6} = 'katpoff';
paramNames{7} = 'kinhon';
paramNames{8} = 'kinhoff';
paramNames{9} = 'kceton';
paramNames{10} = 'kcetoff';
paramNames{11} = 'kadpton';
paramNames{12} = 'kadptoff';
paramNames{13} = 'kdimonSURF';
paramNames{14} = 'kdimonINT';
paramNames{15} = 'kdimoffNOEGF';
paramNames{16} = 'kdimoffEGF';
paramNames{17} = 'kcatNOEGF';
```

```
paramNames{18} = 'kcatEGF';
paramNames{19} = 'kdephosSURF';
paramNames{20} = 'kdephosINT';
paramNames{21} = 'kint';
paramNames{22} = 'kexit';
paramNames{23} = 'ATPconc';
paramNames{24} = 'frecoc';
paramNames{25} = 'frecunoc';
paramNames{26} = 'EGFconc';
paramNames{27} = 'INHconc';
paramNames{28} = 'CETconc';

%dimerization on-rates (calculated)
kdimonSURF = 6.7e-4;
kdimonINT = 2.7e-3;

%parameter values
paramVals(1) = 306; %kegfon MYERS (summarized in WATERS)
paramVals(2) = 0.8; %kegfoff fixed KD (KD from French et al.)
paramVals(3) = 3.1e-4; %kegfonint, 1/(#/endo * min)
paramVals(4) = 0.66; %kegfoffint
paramVals(5) = 1e5; %katpon (diffusion-limited)
paramVals(6) = 1.1e7; %katpoff, computed using steady-state model
paramVals(7) = 1e5; %kinhon (diffusion-limited)
paramVals(8) = 2.1e2; %computed using KD from Wakeling + Gibson, 2002
paramVals(9) = 13.2; %kceton
paramVals(10) = 0.066; %kcetoff
paramVals(11) = kadpton; %kadpton
paramVals(12) = kadptoff; %kadptoff
paramVals(13) = kdimonSURF; %kdimonSURF
paramVals(14) = kdimonINT; %kdimonINT
paramVals(15) = KDdimer*kdimonSURF; %kdimoffNOEGF
paramVals(16) = 1e-1; %kdimoffEGF (Hendriks)
paramVals(17) = 2.7; %kcatNOEGF
paramVals(18) = 13; %kcatEGF
paramVals(19) = NaN; %kdephosSURF
paramVals(20) = NaN; %kdephosINT
paramVals(21) = 0; %ke,model
paramVals(22) = 0.04; %kexit (Hendriks)
paramVals(23) = 1000; %ATPconc
paramVals(24) = 0.5; %frecoc (Hendriks)
paramVals(25) = 0.8; %frecunoc (Hendriks)
paramVals(26) = 0; %EGFconc
paramVals(27) = 0; %INHconc
paramVals(28) = 0; %CETconc
```

```
%compile base model
model = SBmodel('model.txt');
SBPDmakeMEXmodel(model,'mexmodel');
numStatesOutput = SBPDsimulate('mexmodel');
species = length(numStatesOutput.states);

%FITTED PARAMETERS
[tf,indexVec(1)] = ismember('kdephosSURF',paramNames);
[tf,indexVec(2)] = ismember('kdephosINT',paramNames);

paramVals(indexVec(1)) = 5.3e0;
paramVals(indexVec(2)) = 2.2e0;

timecourse(paramNames,paramVals,species,targetEGFR,targetKe,keEGFconc,adpt)

function [] =
timecourse(paramNames,paramVals,species,targetEGFR,targetKe,keEGFconc,adpt)

%expt parameters
STIMconc = 0.00156;
STIMtimeVec = 0:0.01:20;

%relevant indeces
output = SBPDsimulate('mexmodel');
[tf, indexVec(1)] = ismember('E',output.states(1,:));
[tf, indexVec(4)] = ismember('adpt',output.states(1,:));
[tf, indexVec(6)] = ismember('totpEGFRperc',output.variables(1,:));
[tf, indexVec(7)] = ismember('EGFconc',paramNames);

%initial conditions
initConds = zeros(species,1);
initConds(indexVec(1)) = targetEGFR;
initConds(indexVec(4)) = adpt;

%determine ke
errorKe = 1;
tolKe = 0;
while errorKe > tolKe
   [paramVals,errorKe,tolKe] =
correctKe(initConds,paramNames,paramVals,targetKe,keEGFconc);
   [initConds] = steadyStateNODEG(initConds,paramNames,paramVals);
   [keExpt,surfEGFint,intEGF,fity] = calcKe(initConds,paramNames,paramVals,keEGFconc);
   errorKe = abs(keExpt - targetKe);
end

%10 ng/mL EGF timecourse
```

```
paramVals(indexVec(7)) = STIMconc;
EGF10ngmLoutput =
SBPDsimulate('mexmodel',STIMtimeVec,initConds,paramNames,paramVals);
for i = 1:1:length(STIMtimeVec)
   STIM10ngmLsim(i) = EGF10ngmLoutput.variablevalues(i,indexVec(6));
end
paramVals(indexVec(7)) = 0;

%plot results
figure
plot(STIMtimeVec,STIM10ngmLsim,'g','LineWidth',2)
xlabel('time (minutes)')
ylabel('pEGFR/EGFR (%)')

function [paramVals,error,tol] =
correctKe(initConds,paramNames,paramVals,targetKe,keEGFconc)

%gather required indeces
output = SBPDsimulate('mexmodel');
[tf, indexVec(1)] = ismember('kint', paramNames);
[tf, indexVec(2)] = ismember('surfEGF', output.variables(1,:));
[tf, indexVec(3)] = ismember('intEGF', output.variables(1,:));
[tf, indexVec(4)] = ismember('EGFconc', paramNames);

%ke guess
paramVals(indexVec(1)) = targetKe;

%tolerances
tol = targetKe/100;
error = tol*10;
deltaTime = 0.1;
timeVec = 0:deltaTime:7.5;

%set EGF
paramVals(indexVec(4)) = keEGFconc;

%iterate
while error > tol

   output = SBPDsimulate('mexmodel',timeVec,initConds,paramNames,paramVals);

   %first point
   surfEGFint(1) = output.variablevalues(1,indexVec(2));
   intEGF(1) = output.variablevalues(1,indexVec(3));

   %subsequent points
```

```
    for i=2:1:length(timeVec)
        lastPoint = output.variablevalues(i-1,indexVec(2));
        currentPoint = output.variablevalues(i,indexVec(2));
        surfEGFint(i) = 0.5*(currentPoint + lastPoint)*deltaTime + surfEGFint(i-1);
        intEGF(i) = output.variablevalues(i,indexVec(3));
    end

    %fit data
    p = polyfit(surfEGFint,intEGF,1);
    keExpt = p(1);

    %calculate error and generate new guess
    error = abs(keExpt - targetKe);
    kemodel = paramVals(indexVec(1));
    newKe = kemodel/keExpt*targetKe;
    paramVals(indexVec(1)) = newKe;
end

%return EGF conc to zero
paramVals(indexVec(4)) = 0;

function [initConds] = steadyStateNODEG(initConds,paramNames,paramVals)

[tf, indexVec(1)] = ismember('frecoc',paramNames);
[tf, indexVec(2)] = ismember('frecunoc',paramNames);
paramVals(indexVec(1)) = 1;
paramVals(indexVec(2)) = 1;

%steady state time
timeVec = 0:1e9:1e10;

output = SBPDsimulate('mexmodel',timeVec,initConds,paramNames,paramVals);

%extract new initial condition
for i=1:1:length(initConds)
    initConds(i) = output.statevalues(length(timeVec),i);
end

function [keExpt,surfEGFint,intEGF,fity] =
calcKe(initConds,paramNames,paramVals,keEGFconc)

%gather required indeces
output = SBPDsimulate('mexmodel');
[tf, indexVec(1)] = ismember('kint', paramNames);
[tf, indexVec(2)] = ismember('surfEGF', output.variables(1,:));
[tf, indexVec(3)] = ismember('intEGF', output.variables(1,:));
```

```
[tf, indexVec(4)] = ismember('EGFconc', paramNames);

%set EGF
paramVals(indexVec(4)) = keEGFconc;

%simulate EGF timecourse
deltaTime = 0.1;
timeVec = 0:deltaTime:7.5;
output = SBPDsimulate('mexmodel', timeVec, initConds, paramNames, paramVals);

%first point
surfEGFint(1) = output.variablevalues(1,indexVec(2));
intEGF(1) = output.variablevalues(1,indexVec(3));

%subsequent points
for i=2:1:length(timeVec)
   lastPoint = output.variablevalues(i-1,indexVec(2));
   currentPoint = output.variablevalues(i,indexVec(2));
   surfEGFint(i) = 0.5*(currentPoint + lastPoint)*deltaTime + surfEGFint(i-1);
   intEGF(i) = output.variablevalues(i,indexVec(3));
end

%fit data
p = polyfit(surfEGFint,intEGF,1);
keExpt = p(1);

%store fit
for k=1:1:length(timeVec)
   fity(k) = p(1)*surfEGFint(k)+p(2);
end
```

Model topology file (stored as a separate text file):

```
********** MODEL NAME

********** MODEL NOTES

********** MODEL STATE INFORMATION

********** MODEL PARAMETERS

%BINDING
kegfon=0
kegfoff=0
kegfonint=0
kegfoffint=0
kceton=0
kcetoff=0
```

kcetonint=0
kcetoffint=0
katpon=0
katpoff=0
kinhon=0
kinhoff=0
kadpton=0
kadptoff=0

%DIMERIZATION
kdimonSURF=0
kdimonINT=0
kdimoffNOEGF=0
kdimoffEGF=0

%PHOSPHORYLATION
kcatNOEGF=0
kcatEGF=0

%DEPHOSPHORYLATION
kdephosSURF=0
kdephosINT=0

%TRAFFICKING
kint=0
kexit=0
frecoc=0
frecunoc=0

%CONCENTRATIONS
ATPconc=0
EGFconc=0
INHconc=0
CETconc=0

********** MODEL VARIABLES

totEGFR = E + EA + EI + ES + ESA + ESI + EP + EAP + EIP + ESP + ESAP + ESIP + 2*EE + 2*EAEA + 2*EIEI + 2*ESE + 2*ESAEA + 2*ESIEI + 2*ESES + 2*ESAESA + 2*ESIESI + 2*EPEP + 2*EAPEAP + 2*EIPEIP + 2*ESPEP + 2*ESAPEAP + 2*ESIPEIP + 2*ESPESP + 2*ESAPESAP + 2*ESIPESIP + Eint + EAint + EIint + ESint + ESAint + ESIint + EPint + EAPint + EIPint + ESPint + ESAPint + ESIPint + 2*EEint + 2*EAEAint + 2*EIEIint + 2*ESEint + 2*ESAEAint + 2*ESIEIint + 2*ESESint + 2*ESAESAint + 2*ESIESIint + 2*EPEPint + 2*EAPEAPint + 2*EIPEIPint + 2*ESPEPint + 2*ESAPEAPint + 2*ESIPEIPint + 2*ESPESPint + 2*ESAPESAPint + 2*ESIPESIPint + EPadpt + EAPadpt + EIPadpt + ESPadpt + ESAPadpt + ESIPadpt + 2*EPEPadpt + 2*EAPEAPadpt + 2*EIPEIPadpt + 2*ESPEPadpt + 2*ESAPEAPadpt + 2*ESIPEIPadpt + 2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt + EPadptint + EAPadptint + EIPadptint + ESPadptint + ESAPadptint + ESIPadptint + 2*EPEPadptint + 2*EAPEAPadptint + 2*EIPEIPadptint + 2*ESPEPadptint + 2*ESAPEAPadptint + 2*ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint + Ecet + EAcet + EIcet + EPcet + EAPcet + EIPcet + EPcetadpt + EAPcetadpt +

EIPcetadpt + Ecetint + EAcetint + EIcetint + EPcetint + EAPcetint + EIPcetint + EPcetadptint + EAPcetadptint + EIPcetadptint

totpEGFR = EP + EAP + EIP + ESP + ESAP + ESIP + 2*EPEP + 2*EAPEAP + 2*EIPEIP + 2*ESPEP + 2*ESAPEAP + 2*ESIPEIP + 2*ESPESP + 2*ESAPESAP + 2*ESIPESIP + EPint + EAPint + EIPint + ESPint + ESAPint + ESIPint + 2*EPEPint + 2*EAPEAPint + 2*EIPEIPint + 2*ESPEPint + 2*ESAPEAPint + 2*ESIPEIPint + 2*ESPESPint + 2*ESAPESAPint + 2*ESIPESIPint + EPadpt + EAPadpt + EIPadpt + ESPadpt + ESAPadpt + ESIPadpt + 2*EPEPadpt + 2*EAPEAPadpt + 2*EIPEIPadpt + 2*ESPEPadpt + 2*ESAPEAPadpt + 2*ESIPEIPadpt + 2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt + EPadptint + EAPadptint + EIPadptint + ESPadptint + ESAPadptint + ESIPadptint + 2*EPEPadptint + 2*EAPEAPadptint + 2*EIPEIPadptint + 2*ESPEPadptint + 2*ESAPEAPadptint + 2*ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint + EPcet + EAPcet + EIPcet + EPcetadpt + EAPcetadpt + EIPcetadpt + EPcetint + EAPcetint + EIPcetint + EPcetadptint + EAPcetadptint + EIPcetadptint

totpEGFRperc = totpEGFR/totEGFR*100

surfpEGFR = EP + EAP + EIP + ESP + ESAP + ESIP + 2*EPEP + 2*EAPEAP + 2*EIPEIP + 2*ESPEP + 2*ESAPEAP + 2*ESIPEIP + 2*ESPESP + 2*ESAPESAP + 2*ESIPESIP + EPadpt + EAPadpt + EIPadpt + ESPadpt + ESAPadpt + ESIPadpt + 2*EPEPadpt + 2*EAPEAPadpt + 2*EIPEIPadpt + 2*ESPEPadpt + 2*ESAPEAPadpt + 2*ESIPEIPadpt + 2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt + EPcet + EAPcet + EIPcet + EPcetadpt + EAPcetadpt + EIPcetadpt

surfpEGFRperc = surfpEGFR/totpEGFR*100

intpEGFR = EPint + EAPint + EIPint + ESPint + ESAPint + ESIPint + 2*EPEPint + 2*EAPEAPint + 2*EIPEIPint + 2*ESPEPint + 2*ESAPEAPint + 2*ESIPEIPint + 2*ESPESPint + 2*ESAPESAPint + 2*ESIPESIPint + EPadptint + EAPadptint + EIPadptint + ESPadptint + ESAPadptint + ESIPadptint + 2*EPEPadptint + 2*EAPEAPadptint + 2*EIPEIPadptint + 2*ESPEPadptint + 2*ESAPEAPadptint + 2*ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint + EPcetint + EAPcetint + EIPcetint + EPcetadptint + EAPcetadptint + EIPcetadptint

intpEGFRperc = intpEGFR/totpEGFR*100

surfEGF = ES + ESA + ESI + ESP + ESAP + ESIP + ESE + ESAEA + ESIEI + 2*ESES + 2*ESAESA + 2*ESIESI + ESPEP + ESAPEAP + ESIPEIP + 2*ESPESP + 2*ESAPESAP + 2*ESIPESIP + ESPadpt + ESAPadpt + ESIPadpt + ESPEPadpt + ESAPEAPadpt + ESIPEIPadpt + 2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt

intEGF = Sint + debrisEGF + ESint + ESAint + ESIint + ESPint + ESAPint + ESIPint + ESEint + ESAEAint + ESIEIint + 2*ESESint + 2*ESAESAint + 2*ESIESIint + ESPEPint + ESAPEAPint + ESIPEIPint + 2*ESPESPint + 2*ESAPESAPint + 2*ESIPESIPint + ESPadptint + ESAPadptint + ESIPadptint + ESPEPadptint + ESAPEAPadptint + ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint

totEGFRsurf = E + EA + EI + ES + ESA + ESI + EP + EAP + EIP + ESP + ESAP + ESIP + 2*EE + 2*EAEA + 2*EIEI + 2*ESE + 2*ESAEA + 2*ESIEI + 2*ESES + 2*ESAESA + 2*ESIESI + 2*EPEP + 2*EAPEAP + 2*EIPEIP + 2*ESPEP + 2*ESAPEAP + 2*ESIPEIP + 2*ESPESP + 2*ESAPESAP + 2*ESIPESIP + EPadpt + EAPadpt + EIPadpt + ESPadpt + ESAPadpt + ESIPadpt + 2*EPEPadpt + 2*EAPEAPadpt + 2*EIPEIPadpt + 2*ESPEPadpt + 2*ESAPEAPadpt + 2*ESIPEIPadpt +

2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt + Ecet + EAcet + EIcet + EPcet + EAPcet + EIPcet + EPcetadpt + EAPcetadpt + EIPcetadpt

totEGFRsurfperc = totEGFRsurf/totEGFR*100

totEGFRint = Eint + EAint + EIint + ESint + ESAint + ESIint + EPint + EAPint + EIPint + ESPint + ESAPint + ESIPint + 2*EEint + 2*EAEAint + 2*EIEIint + 2*ESEint + 2*ESAEAint + 2*ESIEIint + 2*ESESint + 2*ESAESAint + 2*ESIESIint + 2*EPEPint + 2*EAPEAPint + 2*EIPEIPint + 2*ESPEPint + 2*ESAPEAPint + 2*ESIPEIPint + 2*ESPESPint + 2*ESAPESAPint + 2*ESIPESIPint + EPadptint + EAPadptint + EIPadptint + ESPadptint + ESAPadptint + ESIPadptint + 2*EPEPadptint + 2*EAPEAPadptint + 2*EIPEIPadptint + 2*ESPEPadptint + 2*ESAPEAPadptint + 2*ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint + Ecetint + EAcetint + EIcetint + EPcetint + EAPcetint + EIPcetint + EPcetadptint + EAPcetadptint + EIPcetadptint

totEGFRintperc = totEGFRint/totEGFR*100

surfDimers = 2*EE + 2*EAEA + 2*EIEI + 2*ESE + 2*ESAEA + 2*ESIEI + 2*ESES + 2*ESAESA + 2*ESIESI + 2*EPEP + 2*EAPEAP + 2*EIPEIP + 2*ESPEP + 2*ESAPEAP + 2*ESIPEIP + 2*ESPESP + 2*ESAPESAP + 2*ESIPESIP + 2*EPEPadpt + 2*EAPEAPadpt + 2*EIPEIPadpt + 2*ESPEPadpt + 2*ESAPEAPadpt + 2*ESIPEIPadpt + 2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt

surfDimersPerc = surfDimers/totEGFR*100

intDimers = 2*EEint + 2*EAEAint + 2*EIEIint + 2*ESEint + 2*ESAEAint + 2*ESIEIint + 2*ESESint + 2*ESAESAint + 2*ESIESIint + 2*EPEPint + 2*EAPEAPint + 2*EIPEIPint + 2*ESPEPint + 2*ESAPEAPint + 2*ESIPEIPint + 2*ESPESPint + 2*ESAPESAPint + 2*ESIPESIPint + 2*EPEPadptint + 2*EAPEAPadptint + 2*EIPEIPadptint + 2*ESPEPadptint + 2*ESAPEAPadptint + 2*ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint

intDimersPerc = intDimers/totEGFR*100

totAdpt = adpt + EPadpt + EAPadpt + EIPadpt + ESPadpt + ESAPadpt + ESIPadpt + 2*EPEPadpt + 2*EAPEAPadpt + 2*EIPEIPadpt + 2*ESPEPadpt + 2*ESAPEAPadpt + 2*ESIPEIPadpt + 2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt + EPadptint + EAPadptint + EIPadptint + ESPadptint + ESAPadptint + ESIPadptint + 2*EPEPadptint + 2*EAPEAPadptint + 2*EIPEIPadptint + 2*ESPEPadptint + 2*ESAPEAPadptint + 2*ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint + EPcetadpt + EAPcetadpt + EIPcetadpt + EPcetadptint + EAPcetadptint + EIPcetadptint

totAdptBound = EPadpt + EAPadpt + EIPadpt + ESPadpt + ESAPadpt + ESIPadpt + 2*EPEPadpt + 2*EAPEAPadpt + 2*EIPEIPadpt + 2*ESPEPadpt + 2*ESAPEAPadpt + 2*ESIPEIPadpt + 2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt + EPadptint + EAPadptint + EIPadptint + ESPadptint + ESAPadptint + ESIPadptint + 2*EPEPadptint + 2*EAPEAPadptint + 2*EIPEIPadptint + 2*ESPEPadptint + 2*ESAPEAPadptint + 2*ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint + EPcetadpt + EAPcetadpt + EIPcetadpt + EPcetadptint + EAPcetadptint + EIPcetadptint

totAdptperc = totAdptBound/totEGFR*100

surfAdpt = EPadpt + EAPadpt + EIPadpt + ESPadpt + ESAPadpt + ESIPadpt + 2*EPEPadpt + 2*EAPEAPadpt + 2*EIPEIPadpt + 2*ESPEPadpt + 2*ESAPEAPadpt + 2*ESIPEIPadpt + 2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt + EPcetadpt + EAPcetadpt + EIPcetadpt

surfAdptperc = surfAdpt/totEGFR*100

intAdpt = EPadptint + EAPadptint + EIPadptint + ESPadptint + ESAPadptint + ESIPadptint + 2*EPEPadptint + 2*EAPEAPadptint + 2*EIPEIPadptint + 2*ESPEPadptint + 2*ESAPEAPadptint + 2*ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint + EPcetadptint + EAPcetadptint + EIPcetadptint

intAdptperc = intAdpt/totEGFR*100

occEGFR = ES + ESA + ESI + ESP + ESAP + ESIP + ESE + ESAEA + ESIEI + 2*ESES + 2*ESAESA + 2*ESIESI + ESPEP + ESAPEAP + ESIPEIP + 2*ESPESP + 2*ESAPESAP + 2*ESIPESIP + ESint + ESAint + ESIint + ESPint + ESAPint + ESIPint + ESEint + ESAEAint + ESIEIint + 2*ESESint + 2*ESAESAint + 2*ESIESIint + ESPEPint + ESAPEAPint + ESIPEIPint + 2*ESPESPint + 2*ESAPESAPint + 2*ESIPESIPint + ESPadpt + ESAPadpt + ESIPadpt + ESPEPadpt + ESAPEAPadpt + ESIPEIPadpt + 2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt + ESPadptint + ESAPadptint + ESIPadptint + ESPEPadptint + ESAPEAPadptint + ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint

phosMonomer = EP + EAP + EIP + ESP + ESAP + ESIP + EPint + EAPint + EIPint + ESPint + ESAPint + ESIPint + EPadpt + EAPadpt + EIPadpt + ESPadpt + ESAPadpt + ESIPadpt + EPadptint + EAPadptint + EIPadptint + ESPadptint + ESAPadptint + ESIPadptint + EPcet + EAPcet + EIPcet + EPcetadpt + EAPcetadpt + EIPcetadpt + EPcetint + EAPcetint + EIPcetint + EPcetadptint + EAPcetadptint + EIPcetadptint

occMon = ES + ESA + ESI + ESP + ESAP + ESIP + ESint + ESAint + ESIint + ESPint + ESAPint + ESIPint + ESPadpt + ESAPadpt + ESIPadpt + ESPadptint + ESAPadptint + ESIPadptint

occDim = 2*ESE + 2*ESAEA + 2*ESIEI + 2*ESES + 2*ESAESA + 2*ESIESI + 2*ESPEP + 2*ESAPEAP + 2*ESIPEIP + 2*ESPESP + 2*ESAPESAP + 2*ESIPESIP + 2*ESEint + 2*ESAEAint + 2*ESIEIint + 2*ESESint + 2*ESAESAint + 2*ESIESIint + 2*ESPEPint + 2*ESAPEAPint + 2*ESIPEIPint + 2*ESPESPint + 2*ESAPESAPint + 2*ESIPESIPint + 2*ESPEPadpt + 2*ESAPEAPadpt + 2*ESIPEIPadpt + 2*ESPESPadpt + 2*ESAPESAPadpt + 2*ESIPESIPadpt + 2*ESPEPadptint + 2*ESAPEAPadptint + 2*ESIPEIPadptint + 2*ESPESPadptint + 2*ESAPESAPadptint + 2*ESIPESIPadptint

unoccMon = E + EA + EI + EP + EAP + EIP + Eint + EAint + EIint + EPint + EAPint + EIPint+ EPadpt + EAPadpt + EIPadpt + EPadptint + EAPadptint + EIPadptint + Ecet + EAcet + EIcet + EPcet + EAPcet + EIPcet + EPcetadpt + EAPcetadpt + EIPcetadpt + Ecetint + EAcetint + EIcetint + EPcetint + EAPcetint + EIPcetint + EPcetadptint + EAPcetadptint + EIPcetadptint

unoccDim = 2*EE + 2*EAEA + 2*EIEI + 2*EPEP + 2*EAPEAP + 2*EIPEIP + 2*EEint + 2*EAEAint + 2*EIEIint + 2*EPEPint + 2*EAPEAPint + 2*EIPEIPint + 2*EPEPadpt + 2*EAPEAPadpt + 2*EIPEIPadpt + 2*EPEPadptint + 2*EAPEAPadptint + 2*EIPEIPadptint

********** MODEL REACTIONS

%CETUXIMAB BINDING

```
E<=>Ecet : Cetuximab Binding Surface 1
        vf=kceton*CETconc*E
        vr=kcetoff*Ecet

EA<=>EAcet : Cetuximab Binding Surface 2
        vf=kceton*CETconc*EA
        vr=kcetoff*EAcet

EI<=>EIcet : Cetuximab Binding Surface 3
        vf=kceton*CETconc*EI
        vr=kcetoff*EIcet

EP<=>EPcet : Cetuximab Binding Surface 4
        vf=kceton*CETconc*EP
        vr=kcetoff*EPcet

EAP<=>EAPcet : Cetuximab Binding Surface 5
        vf=kceton*CETconc*EAP
        vr=kcetoff*EAPcet

EIP<=>EIPcet : Cetuximab Binding Surface 6
        vf=kceton*CETconc*EIP
        vr=kcetoff*EIPcet

EPadpt<=>EPcetadpt : Cetuximab Binding Surface 13
        vf=kceton*CETconc*EPadpt
        vr=kcetoff*EPcetadpt

EAPadpt<=>EAPcetadpt : Cetuximab Binding Surface 14
        vf=kceton*CETconc*EAPadpt
        vr=kcetoff*EAPcetadpt

EIPadpt<=>EIPcetadpt : Cetuximab Binding Surface 15
        vf=kceton*CETconc*EIPadpt
        vr=kcetoff*EIPcetadpt

%ATP BINDING TO MONOMERS AT THE SURFACE

E<=>EA : Monomer ATP Binding 1
        vf=katpon*ATPconc*E
        vr=katpoff*EA

ES<=>ESA : Monomer ATP Binding 2
        vf=katpon*ATPconc*ES
        vr=katpoff*ESA

EP<=>EAP : Monomer ATP Binding 3
        vf=katpon*EP*ATPconc
        vr=katpoff*EAP
```

ESP<=>ESAP : Monomer ATP Binding 4
vf=katpon*ESP*ATPconc
vr=katpoff*ESAP

EPadpt<=>EAPadpt : Monomer ATP Binding 9
vf=katpon*EPadpt*ATPconc
vr=katpoff*EAPadpt

ESPadpt<=>ESAPadpt : Monomer ATP Binding 10
vf=katpon*ESPadpt*ATPconc
vr=katpoff*ESAPadpt

Ecet<=>EAcet : Monomer ATP Binding 13
vf=katpon*ATPconc*Ecet
vr=katpoff*EAcet

EPcet<=>EAPcet : Monomer ATP Binding 14
vf=katpon*ATPconc*EPcet
vr=katpoff*EAPcet

EPcetadpt<=>EAPcetadpt : Monomer ATP Binding 17
vf=katpon*ATPconc*EPcetadpt
vr=katpoff*EAPcetadpt

%INH BINDING TO MONOMERS AT THE SURFACE

E<=>EI : Monomer Inhibitor Binding 1
vf=kinhon*E*INHconc
vr=kinhoff*EI

ES<=>ESI : Monomer Inhibitor Binding 2
vf=kinhon*ES*INHconc
vr=kinhoff*ESI

EP<=>EIP : Monomer Inhibitor Binding 3
vf=kinhon*EP*INHconc
vr=kinhoff*EIP

ESP<=>ESIP : Monomer Inhibitor Binding 4
vf=kinhon*ESP*INHconc
vr=kinhoff*ESIP

EPadpt<=>EIPadpt : Monomer Inhibitor Binding 9
vf=kinhon*EPadpt*INHconc
vr=kinhoff*EIPadpt

ESPadpt<=>ESIPadpt : Monomer Inhibitor Binding 10
vf=kinhon*ESPadpt*INHconc
vr=kinhoff*ESIPadpt

Ecet<=>EIcet : Monomer Inhibitor Binding 13

```
        vf=kinhon*INHconc*Ecet
        vr=kinhoff*EIcet

EPcet<=>EIPcet : Monomer Inhibitor Binding 14
        vf=kinhon*INHconc*EPcet
        vr=kinhoff*EIPcet

EPcetadpt<=>EIPcetadpt : Monomer Inhibitor Binding 17
        vf=kinhon*INHconc*EPcetadpt
        vr=kinhoff*EIPcetadpt

%LIGAND BINDING TO MONOMERS AT THE SURFACE

E<=>ES : Monomer EGF Binding 1
        vf=kegfon*EGFconc*E
        vr=kegfoff*ES

EA<=>ESA : Monomer EGF Binding 2
        vf=kegfon*EGFconc*EA
        vr=kegfoff*ESA

EI<=>ESI : Monomer EGF Binding 3
        vf=kegfon*EGFconc*EI
        vr=kegfoff*ESI

EP<=>ESP : Monomer EGF Binding 4
        vf=kegfon*EGFconc*EP
        vr=kegfoff*ESP

EAP<=>ESAP : Monomer EGF Binding 5
        vf=kegfon*EGFconc*EAP
        vr=kegfoff*ESAP

EIP<=>ESIP : Monomer EGF Binding 6
        vf=kegfon*EGFconc*EIP
        vr=kegfoff*ESIP

EPadpt<=>ESPadpt : Monomer EGF Binding 13
        vf=kegfon*EGFconc*EPadpt
        vr=kegfoff*ESPadpt

EAPadpt<=>ESAPadpt : Monomer EGF Binding 14
        vf=kegfon*EGFconc*EAPadpt
        vr=kegfoff*ESAPadpt

EIPadpt<=>ESIPadpt : Monomer EGF Binding 15
        vf=kegfon*EGFconc*EIPadpt
        vr=kegfoff*ESIPadpt

%DIMERIZATION IN THE ABSENSE OF EGF AT THE SURFACE
```

E+E<=>EE : Dimerization no EGF 1
vf=kdimonSURF*E*E
vr=kdimoffNOEGF*EE

EA+EA<=>EAEA : Dimerization no EGF 2
vf=kdimonSURF*EA*EA
vr=kdimoffNOEGF*EAEA

EI+EI<=>EIEI : Dimerization no EGF 3
vf=kdimonSURF*EI*EI
vr=kdimoffNOEGF*EIEI

EP+EP<=>EPEP : Dimerization no EGF 4
vf=kdimonSURF*EP*EP
vr=kdimoffNOEGF*EPEP

EAP+EAP<=>EAPEAP : Dimerization no EGF 5
vf=kdimonSURF*EAP*EAP
vr=kdimoffNOEGF*EAPEAP

EIP+EIP<=>EIPEIP : Dimerization no EGF 6
vf=kdimonSURF*EIP*EIP
vr=kdimoffNOEGF*EIPEIP

EPadpt+EPadpt<=>EPEPadpt : Dimerization no EGF 13
vf=kdimonSURF*EPadpt*EPadpt
vr=kdimoffNOEGF*EPEPadpt

EAPadpt+EAPadpt<=>EAPEAPadpt : Dimerization no EGF 14
vf=kdimonSURF*EAPadpt*EAPadpt
vr=kdimoffNOEGF*EAPEAPadpt

EIPadpt+EIPadpt<=>EIPEIPadpt : Dimerization no EGF 15
vf=kdimonSURF*EIPadpt*EIPadpt
vr=kdimoffNOEGF*EIPEIPadpt

%ASSYMETRIC DIMERIZATION AT THE SURFACE

ES+E<=>ESE : Surface Dimerization Assymetric 1
vf=kdimonSURF*ES*E
vr=kdimoffEGF*ESE

ESA+EA<=>ESAEA : Surface Dimerization Assymetric 2
vf=kdimonSURF*ESA*EA
vr=kdimoffEGF*ESAEA

ESI+EI<=>ESIEI : Surface Dimerization Assymetric 3
vf=kdimonSURF*ESI*EI
vr=kdimoffEGF*ESIEI

ESP+EP<=>ESPEP : Surface Dimerization Assymetric 4

vf=kdimonSURF*ESP*EP
vr=kdimoffEGF*ESPEP

ESAP+EAP<=>ESAPEAP : Surface Dimerization Assymetric 5
vf=kdimonSURF*ESAP*EAP
vr=kdimoffEGF*ESAPEAP

ESIP+EIP<=>ESIPEIP : Surface Dimerization Assymetric 6
vf=kdimonSURF*ESIP*EIP
vr=kdimoffEGF*ESIPEIP

ESPadpt+EPadpt<=>ESPEPadpt : Surface Dimerization Assymetric 13
vf=kdimonSURF*ESPadpt*EPadpt
vr=kdimoffEGF*ESPEPadpt

ESAPadpt+EAPadpt<=>ESAPEAPadpt : Surface Dimerization Assymetric 14
vf=kdimonSURF*ESAPadpt*EAPadpt
vr=kdimoffEGF*ESAPEAPadpt

ESIPadpt+EIPadpt<=>ESIPEIPadpt : Surface Dimerization Assymetric 15
vf=kdimonSURF*ESIPadpt*EIPadpt
vr=kdimoffEGF*ESIPEIPadpt

%DIMERIZATION IN THE PRESENCE OF EGF AT THE SURFACE

ES+ES<=>ESES : Dimerization EGF 1
vf=kdimonSURF*ES*ES
vr=kdimoffEGF*ESES

ESA+ESA<=>ESAESA : Dimerization EGF 2
vf=kdimonSURF*ESA*ESA
vr=kdimoffEGF*ESAESA

ESI+ESI<=>ESIESI : Dimerization EGF 3
vf=kdimonSURF*ESI*ESI
vr=kdimoffEGF*ESIESI

ESP+ESP<=>ESPESP : Dimerization EGF 4
vf=kdimonSURF*ESP*ESP
vr=kdimoffEGF*ESPESP

ESAP+ESAP<=>ESAPESAP : Dimerization EGF 5
vf=kdimonSURF*ESAP*ESAP
vr=kdimoffEGF*ESAPESAP

ESIP+ESIP<=>ESIPESIP : Dimerization EGF 6
vf=kdimonSURF*ESIP*ESIP
vr=kdimoffEGF*ESIPESIP

ESPadpt+ESPadpt<=>ESPESPadpt : Dimerization EGF 13
vf=kdimonSURF*ESPadpt*ESPadpt

vr=kdimoffEGF*ESPESPadpt

ESAPadpt+ESAPadpt<=>ESAPESAPadpt : Dimerization EGF 14
vf=kdimonSURF*ESAPadpt*ESAPadpt
vr=kdimoffEGF*ESAPESAPadpt

ESIPadpt+ESIPadpt<=>ESIPESIPadpt : Dimerization EGF 15
vf=kdimonSURF*ESIPadpt*ESIPadpt
vr=kdimoffEGF*ESIPESIPadpt

%DIMER ATP BINDING AT THE SURFACE

EE<=>EAEA : Dimer ATP Binding 1
vf=katpon*EE*ATPconc
vr=katpoff*EAEA

ESE<=>ESAEA : Dimer ATP Binding 2
vf=katpon*ESE*ATPconc
vr=katpoff*ESAEA

ESES<=>ESAESA : Dimer ATP Binding 3
vf=katpon*ESES*ATPconc
vr=katpoff*ESAESA

EPEP<=>EAPEAP : Dimer ATP Binding 4
vf=katpon*EPEP*ATPconc
vr=katpoff*EAPEAP

ESPEP<=>ESAPEAP : Dimer ATP Binding 5
vf=katpon*ESPEP*ATPconc
vr=katpoff*ESAPEAP

ESPESP<=>ESAPESAP : Dimer ATP Binding 6
vf=katpon*ESPESP*ATPconc
vr=katpoff*ESAPESAP

EPEPadpt<=>EAPEAPadpt : Dimer ATP Binding 13
vf=katpon*EPEPadpt*ATPconc
vr=katpoff*EAPEAPadpt

ESPEPadpt<=>ESAPEAPadpt : Dimer ATP Binding 14
vf=katpon*ESPEPadpt*ATPconc
vr=katpoff*ESAPEAPadpt

ESPESPadpt<=>ESAPESAPadpt : Dimer ATP Binding 15
vf=katpon*ESPESPadpt*ATPconc
vr=katpoff*ESAPESAPadpt

%DIMER INH BINDING AT THE SURFACE

EE<=>EIEI : Dimer INH Binding 1

```
        vf=kinhon*EE*INHconc
        vr=kinhoff*EIEI

ESE<=>ESIEI : Dimer INH Binding 2
        vf=kinhon*ESE*INHconc
        vr=kinhoff*ESIEI

ESES<=>ESIESI : Dimer INH Binding 3
        vf=kinhon*ESES*INHconc
        vr=kinhoff*ESIESI

EPEP<=>EIPEIP : Dimer INH Binding 4
        vf=kinhon*EPEP*INHconc
        vr=kinhoff*EIPEIP

ESPEP<=>ESIPEIP : Dimer INH Binding 5
        vf=kinhon*ESPEP*INHconc
        vr=kinhoff*ESIPEIP

ESPESP<=>ESIPESIP : Dimer INH Binding 6
        vf=kinhon*ESPESP*INHconc
        vr=kinhoff*ESIPESIP

EPEPadpt<=>EIPEIPadpt : Dimer INH Binding 13
        vf=kinhon*EPEPadpt*INHconc
        vr=kinhoff*EIPEIPadpt

ESPEPadpt<=>ESIPEIPadpt : Dimer INH Binding 14
        vf=kinhon*ESPEPadpt*INHconc
        vr=kinhoff*ESIPEIPadpt

ESPESPadpt<=>ESIPESIPadpt : Dimer INH Binding 15
        vf=kinhon*ESPESPadpt*INHconc
        vr=kinhoff*ESIPESIPadpt

%DIMER EGF BINDING AT THE SURFACE

EE<=>ESE : Dimer EGF Binding 1
        vf=2*kegfon*EGFconc*EE
        vr=kegfoff*ESE

ESE<=>ESES : Dimer EGF Binding 2
        vf=kegfon*EGFconc*ESE
        vr=kegfoff*ESES

EAEA<=>ESAEA : Dimer EGF Binding 3
        vf=2*kegfon*EGFconc*EAEA
        vr=kegfoff*ESAEA

ESAEA<=>ESAESA : Dimer EGF Binding 4
        vf=kegfon*EGFconc*ESAEA
```

vr=kegfoff*ESAESA

EIEI<=>ESIEI : Dimer EGF Binding 5
vf=2*kegfon*EGFconc*EIEI
vr=kegfoff*ESIEI

ESIEI<=>ESIESI : Dimer EGF Binding 6
vf=kegfon*EGFconc*ESIEI
vr=kegfoff*ESIESI

EPEP<=>ESPEP : Dimer EGF Binding 7
vf=2*kegfon*EGFconc*EPEP
vr=kegfoff*ESPEP

ESPEP<=>ESPESP : Dimer EGF Binding 8
vf=kegfon*EGFconc*ESPEP
vr=kegfoff*ESPESP

EAPEAP<=>ESAPEAP : Dimer EGF Binding 9
vf=2*kegfon*EGFconc*EAPEAP
vr=kegfoff*ESAPEAP

ESAPEAP<=>ESAPESAP : Dimer EGF Binding 10
vf=kegfon*EGFconc*ESAPEAP
vr=kegfoff*ESAPESAP

EIPEIP<=>ESIPEIP : Dimer EGF Binding 11
vf=2*kegfon*EGFconc*EIPEIP
vr=kegfoff*ESIPEIP

ESIPEIP<=>ESIPESIP : Dimer EGF Binding 12
vf=kegfon*EGFconc*ESIPEIP
vr=kegfoff*ESIPESIP

EPEPadpt<=>ESPEPadpt : Dimer EGF Binding 25
vf=2*kegfon*EGFconc*EPEPadpt
vr=kegfoff*ESPEPadpt

ESPEPadpt<=>ESPESPadpt : Dimer EGF Binding 26
vf=kegfon*EGFconc*ESPEPadpt
vr=kegfoff*ESPESPadpt

EAPEAPadpt<=>ESAPEAPadpt : Dimer EGF Binding 27
vf=2*kegfon*EGFconc*EAPEAPadpt
vr=kegfoff*ESAPEAPadpt

ESAPEAPadpt<=>ESAPESAPadpt : Dimer EGF Binding 28
vf=kegfon*EGFconc*ESAPEAPadpt
vr=kegfoff*ESAPESAPadpt

EIPEIPadpt<=>ESIPEIPadpt : Dimer EGF Binding 29

```
        vf=2*kegfon*EGFconc*EIPEIPadpt
        vr=kegfoff*ESIPEIPadpt

ESIPEIPadpt<=>ESIPESIPadpt : Dimer EGF Binding 30
        vf=kegfon*EGFconc*ESIPEIPadpt
        vr=kegfoff*ESIPESIPadpt


%PHOSPHORYLATION AT THE SURFACE

EAEA=>EPEP : Phosphorylation 1
        vf=kcatNOEGF*EAEA

ESAEA=>ESPEP : Phosphorylation 2
        vf=kcatEGF*ESAEA

ESAESA=>ESPESP : Phosphorylation 3
        vf=kcatEGF*ESAESA

%DEPHOSPHORYLATION AT THE SURFACE

EP=>E : Dephosphorylation 1
        vf=kdephosSURF*EP

EAP=>EA : Dephosphorylation 2
        vf=kdephosSURF*EAP

EIP=>EI : Dephosphorylation 3
        vf=kdephosSURF*EIP

ESP=>ES : Dephosphorylation 4
        vf=kdephosSURF*ESP

ESAP=>ESA : Dephosphorylation 5
        vf=kdephosSURF*ESAP

ESIP=>ESI : Dephosphorylation 6
        vf=kdephosSURF*ESIP

EPEP=>EE : Dephosphorylation 7
        vf=kdephosSURF*EPEP

EAPEAP=>EAEA : Dephosphorylation 8
        vf=kdephosSURF*EAPEAP

EIPEIP=>EIEI : Dephosphorylation 9
        vf=kdephosSURF*EIPEIP

ESPEP=>ESE : Dephosphorylation 10
        vf=kdephosSURF*ESPEP
```

ESAPEAP=>ESAEA : Dephosphorylation 11
vf=kdephosSURF*ESAPEAP

ESIPEIP=>ESIEI : Dephosphorylation 12
vf=kdephosSURF*ESIPEIP

ESPESP=>ESES : Dephosphorylation 13
vf=kdephosSURF*ESPESP

ESAPESAP=>ESAESA : Dephosphorylation 14
vf=kdephosSURF*ESAPESAP

ESIPESIP=>ESIESI : Dephosphorylation 15
vf=kdephosSURF*ESIPESIP

EPcet=>Ecet : Dephosphorylation 31
vf=kdephosSURF*EPcet

EAPcet=>EAcet : Dephosphorylation 32
vf=kdephosSURF*EAPcet

EIPcet=>EIcet : Dephosphorylation 33
vf=kdephosSURF*EIPcet

%ADAPTER BINDING AT THE SURFACE

EP+adpt<=>EPadpt : Surface Adapter Binding 1
vf=kadpton*EP*adpt
vr=kadptoff*EPadpt

EAP+adpt<=>EAPadpt : Surface Adapter Binding 2
vf=kadpton*EAP*adpt
vr=kadptoff*EAPadpt

EIP+adpt<=>EIPadpt : Surface Adapter Binding 3
vf=kadpton*EIP*adpt
vr=kadptoff*EIPadpt

ESP+adpt<=>ESPadpt : Surface Adapter Binding 4
vf=kadpton*ESP*adpt
vr=kadptoff*ESPadpt

ESAP+adpt<=>ESAPadpt : Surface Adapter Binding 5
vf=kadpton*ESAP*adpt
vr=kadptoff*ESAPadpt

ESIP+adpt<=>ESIPadpt : Surface Adapter Binding 6
vf=kadpton*ESIP*adpt
vr=kadptoff*ESIPadpt

EPEP+2*adpt<=>EPEPadpt : Surface Adapter Binding 7

vf=kadpton*EPEP*adpt
vr=kadptoff*EPEPadpt

EAPEAP+2*adpt<=>EAPEAPadpt : Surface Adapter Binding 8
vf=kadpton*EAPEAP*adpt
vr=kadptoff*EAPEAPadpt

EIPEIP+2*adpt<=>EIPEIPadpt : Surface Adapter Binding 9
vf=kadpton*EIPEIP*adpt
vr=kadptoff*EIPEIPadpt

ESPEP+2*adpt<=>ESPEPadpt : Surface Adapter Binding 10
vf=kadpton*ESPEP*adpt
vr=kadptoff*ESPEPadpt

ESAPEAP+2*adpt<=>ESAPEAPadpt : Surface Adapter Binding 11
vf=kadpton*ESAPEAP*adpt
vr=kadptoff*ESAPEAPadpt

ESIPEIP+2*adpt<=>ESIPEIPadpt : Surface Adapter Binding 12
vf=kadpton*ESIPEIP*adpt
vr=kadptoff*ESIPEIPadpt

ESPESP+2*adpt<=>ESPESPadpt : Surface Adapter Binding 13
vf=kadpton*ESPESP*adpt
vr=kadptoff*ESPESPadpt

ESAPESAP+2*adpt<=>ESAPESAPadpt : Surface Adapter Binding 14
vf=kadpton*ESAPESAP*adpt
vr=kadptoff*ESAPESAPadpt

ESIPESIP+2*adpt<=>ESIPESIPadpt : Surface Adapter Binding 15
vf=kadpton*ESIPESIP*adpt
vr=kadptoff*ESIPESIPadpt

EPcet+adpt<=>EPcetadpt : Surface Adapter Binding 31
vf=kadpton*EPcet*adpt
vr=kadptoff*EPcetadpt

EAPcet+adpt<=>EAPcetadpt : Surface Adapter Binding 32
vf=kadpton*EAPcet*adpt
vr=kadptoff*EAPcetadpt

EIPcet+adpt<=>EIPcetadpt : Surface Adapter Binding 33
vf=kadpton*EIPcet*adpt
vr=kadptoff*EIPcetadpt

%INTERNALIZATION

EPadpt=>EPadptint : Internalization 31
vf=kint*EPadpt

EAPadpt=>EAPadptint : Internalization 32
vf=kint*EAPadpt

EIPadpt=>EIPadptint : Internalization 33
vf=kint*EIPadpt

ESPadpt=>ESPadptint : Internalization 34
vf=kint*ESPadpt

ESAPadpt=>ESAPadptint : Internalization 35
vf=kint*ESAPadpt

ESIPadpt=>ESIPadptint : Internalization 36
vf=kint*ESIPadpt

EPEPadpt=>EPEPadptint : Internalization 37
vf=kint*EPEPadpt

EAPEAPadpt=>EAPEAPadptint : Internalization 38
vf=kint*EAPEAPadpt

EIPEIPadpt=>EIPEIPadptint : Internalization 39
vf=kint*EIPEIPadpt

ESPEPadpt=>ESPEPadptint : Internalization 40
vf=kint*ESPEPadpt

ESAPEAPadpt=>ESAPEAPadptint : Internalization 41
vf=kint*ESAPEAPadpt

ESIPEIPadpt=>ESIPEIPadptint : Internalization 42
vf=kint*ESIPEIPadpt

ESPESPadpt=>ESPESPadptint : Internalization 43
vf=kint*ESPESPadpt

ESAPESAPadpt=>ESAPESAPadptint : Internalization 44
vf=kint*ESAPESAPadpt

ESIPESIPadpt=>ESIPESIPadptint : Internalization 45
vf=kint*ESIPESIPadpt

EPcetadpt=>EPcetadptint : Internalization 52
vf=kint*EPcetadpt

EAPcetadpt=>EAPcetadptint : Internalization 53
vf=kint*EAPcetadpt

EIPcetadpt=>EIPcetadptint : Internalization 54
vf=kint*EIPcetadpt

%ATP BINDING TO MONOMERS IN THE ENDOSOME

Eint<=>EAint : Internal Monomer ATP Binding 1
vf=katpon*Eint*ATPconc
vr=katpoff*EAint

ESint<=>ESAint : Internal Monomer ATP Binding 2
vf=katpon*ESint*ATPconc
vr=katpoff*ESAint

EPint<=>EAPint : Internal Monomer ATP Binding 3
vf=katpon*EPint*ATPconc
vr=katpoff*EAPint

ESPint<=>ESAPint : Internal Monomer ATP Binding 4
vf=katpon*ESPint*ATPconc
vr=katpoff*ESAPint

EPadptint<=>EAPadptint : Internal Monomer ATP Binding 5
vf=katpon*EPadptint*ATPconc
vr=katpoff*EAPadptint

ESPadptint<=>ESAPadptint : Internal Monomer ATP Binding 6
vf=katpon*ESPadptint*ATPconc
vr=katpoff*ESAPadptint

Ecetint<=>EAcetint : Internal Monomer ATP Binding 7
vf=katpon*Ecetint*ATPconc
vr=katpoff*EAcetint

EPcetint<=>EAPcetint : Internal Monomer ATP Binding 8
vf=katpon*EPcetint*ATPconc
vr=katpoff*EAPcetint

EPcetadptint<=>EAPcetadptint : Internal Monomer ATP Binding 9
vf=katpon*EPcetadptint*ATPconc
vr=katpoff*EAPcetadptint

%INH BINDING TO MONOMERS IN THE ENDOSOME

Eint<=>EIint : Internal Monomer Inhibitor Binding 1
vf=kinhon*Eint*INHconc
vr=kinhoff*EIint

ESint<=>ESIint : Internal Monomer Inhibitor Binding 2
vf=kinhon*ESint*INHconc
vr=kinhoff*ESIint

EPint<=>EIPint : Internal Monomer Inhibitor Binding 3
vf=kinhon*EPint*INHconc

vr=kinhoff*EIPint

ESPint<=>ESIPint : Internal Monomer Inhibitor Binding 4
vf=kinhon*ESPint*INHconc
vr=kinhoff*ESIPint

EPadptint<=>EIPadptint : Internal Monomer Inhibitor Binding 5
vf=kinhon*EPadptint*INHconc
vr=kinhoff*EIPadptint

ESPadptint<=>ESIPadptint : Internal Monomer Inhibitor Binding 6
vf=kinhon*ESPadptint*INHconc
vr=kinhoff*ESIPadptint

Ecetint<=>EIcetint : Internal Monomer Inhibitor Binding 7
vf=kinhon*Ecetint*INHconc
vr=kinhoff*EIcetint

EPcetint<=>EIPcetint : Internal Monomer Inhibitor Binding 8
vf=kinhon*EPcetint*INHconc
vr=kinhoff*EIPcetint

EPcetadptint<=>EIPcetadptint : Internal Monomer Inhibitor Binding 9
vf=kinhon*EPcetadptint*INHconc
vr=kinhoff*EIPcetadptint

%LIGAND BINDING TO MONOMERS IN THE ENDOSOME

Eint+Sint<=>ESint : Internal Monomer EGF Binding 1
vf=kegfonint*Eint*Sint
vr=kegfoffint*ESint

EAint+Sint<=>ESAint : Internal Monomer EGF Binding 2
vf=kegfonint*EAint*Sint
vr=kegfoffint*ESAint

EIint+Sint<=>ESIint : Internal Monomer EGF Binding 3
vf=kegfonint*EIint*Sint
vr=kegfoffint*ESIint

EPint+Sint<=>ESPint : Internal Monomer EGF Binding 4
vf=kegfonint*EPint*Sint
vr=kegfoffint*ESPint

EAPint+Sint<=>ESAPint : Internal Monomer EGF Binding 5
vf=kegfonint*EAPint*Sint
vr=kegfoffint*ESAPint

EIPint+Sint<=>ESIPint : Internal Monomer EGF Binding 6
vf=kegfonint*EIPint*Sint
vr=kegfoffint*ESIPint

EPadptint+Sint<=>ESPadptint : Internal Monomer EGF Binding 7
vf=kegfonint*EPadptint*Sint
vr=kegfoffint*ESPadptint

EAPadptint+Sint<=>ESAPadptint : Internal Monomer EGF Binding 8
vf=kegfonint*EAPadptint*Sint
vr=kegfoffint*ESAPadptint

EIPadptint+Sint<=>ESIPadptint : Internal Monomer EGF Binding 9
vf=kegfonint*EIPadptint*Sint
vr=kegfoffint*ESIPadptint

%DIMERIZATION IN THE ABSENSE OF EGF IN THE ENDOSOME

Eint+Eint<=>EEint : Internal Dimerization no EGF 1
vf=kdimonINT*Eint*Eint
vr=kdimoffNOEGF*EEint

EAint+EAint<=>EAEAint : Internal Dimerization no EGF 2
vf=kdimonINT*EAint*EAint
vr=kdimoffNOEGF*EAEAint

EIint+EIint<=>EIEIint : Internal Dimerization no EGF 3
vf=kdimonINT*EIint*EIint
vr=kdimoffNOEGF*EIEIint

EPint+EPint<=>EPEPint : Internal Dimerization no EGF 4
vf=kdimonINT*EPint*EPint
vr=kdimoffNOEGF*EPEPint

EAPint+EAPint<=>EAPEAPint : Internal Dimerization no EGF 5
vf=kdimonINT*EAPint*EAPint
vr=kdimoffNOEGF*EAPEAPint

EIPint+EIPint<=>EIPEIPint : Internal Dimerization no EGF 6
vf=kdimonINT*EIPint*EIPint
vr=kdimoffNOEGF*EIPEIPint

EPadptint+EPadptint<=>EPEPadptint : Internal Dimerization no EGF 7
vf=kdimonINT*EPadptint*EPadptint
vr=kdimoffNOEGF*EPEPadptint

EAPadptint+EAPadptint<=>EAPEAPadptint : Internal Dimerization no EGF 8
vf=kdimonINT*EAPadptint*EAPadptint
vr=kdimoffNOEGF*EAPEAPadptint

EIPadptint+EIPadptint<=>EIPEIPadptint : Internal Dimerization no EGF 9
vf=kdimonINT*EIPadptint*EIPadptint
vr=kdimoffNOEGF*EIPEIPadptint

%ASSYMETRIC DIMERIZATION IN THE ENDOSOME

ESint+Eint<=>ESEint : Internal Dimerization Assymetric 1
vf=kdimonINT*ESint*Eint
vr=kdimoffEGF*ESEint

ESAint+EAint<=>ESAEAint : Internal Dimerization Assymetric 2
vf=kdimonINT*ESAint*EAint
vr=kdimoffEGF*ESAEAint

ESIint+EIint<=>ESIEIint : Internal Dimerization Assymetric 3
vf=kdimonINT*ESIint*EIint
vr=kdimoffEGF*ESIEIint

ESPint+EPint<=>ESPEPint : Internal Dimerization Assymetric 4
vf=kdimonINT*ESPint*EPint
vr=kdimoffEGF*ESPEPint

ESAPint+EAPint<=>ESAPEAPint : Internal Dimerization Assymetric 5
vf=kdimonINT*ESAPint*EAPint
vr=kdimoffEGF*ESAPEAPint

ESIPint+EIPint<=>ESIPEIPint : Internal Dimerization Assymetric 6
vf=kdimonINT*ESIPint*EIPint
vr=kdimoffEGF*ESIPEIPint

ESPadptint+EPadptint<=>ESPEPadptint : Internal Dimerization Assymetric 7
vf=kdimonINT*ESPadptint*EPadptint
vr=kdimoffEGF*ESPEPadptint

ESAPadptint+EAPadptint<=>ESAPEAPadptint : Internal Dimerization Assymetric 8
vf=kdimonINT*ESAPadptint*EAPadptint
vr=kdimoffEGF*ESAPEAPadptint

ESIPadptint+EIPadptint<=>ESIPEIPadptint : Internal Dimerization Assymetric 9
vf=kdimonINT*ESIPadptint*EIPadptint
vr=kdimoffEGF*ESIPEIPadptint

%DIMERIZATION IN THE PRESENCE OF EGF IN THE ENDOSOME

ESint+ESint<=>ESESint : Internal Dimerization EGF 1
vf=kdimonINT*ESint*ESint
vr=kdimoffEGF*ESESint

ESAint+ESAint<=>ESAESAint : Internal Dimerization EGF 2
vf=kdimonINT*ESAint*ESAint
vr=kdimoffEGF*ESAESAint

ESIint+ESIint<=>ESIESIint : Internal Dimerization EGF 3
vf=kdimonINT*ESIint*ESIint
vr=kdimoffEGF*ESIESIint

ESPint+ESPint<=>ESPESPint : Internal Dimerization EGF 4
vf=kdimonINT*ESPint*ESPint
vr=kdimoffEGF*ESPESPint

ESAPint+ESAPint<=>ESAPESAPint : Internal Dimerization EGF 5
vf=kdimonINT*ESAPint*ESAPint
vr=kdimoffEGF*ESAPESAPint

ESIPint+ESIPint<=>ESIPESIPint : Internal Dimerization EGF 6
vf=kdimonINT*ESIPint*ESIPint
vr=kdimoffEGF*ESIPESIPint

ESPadptint+ESPadptint<=>ESPESPadptint : Internal Dimerization EGF 7
vf=kdimonINT*ESPadptint*ESPadptint
vr=kdimoffEGF*ESPESPadptint

ESAPadptint+ESAPadptint<=>ESAPESAPadptint : Internal Dimerization EGF 8
vf=kdimonINT*ESAPadptint*ESAPadptint
vr=kdimoffEGF*ESAPESAPadptint

ESIPadptint+ESIPadptint<=>ESIPESIPadptint : Internal Dimerization EGF 9
vf=kdimonINT*ESIPadptint*ESIPadptint
vr=kdimoffEGF*ESIPESIPadptint

%DIMER ATP BINDING IN THE ENDOSOME

EEint<=>EAEAint : Internal Dimer ATP Binding 1
vf=katpon*EEint*ATPconc
vr=katpoff*EAEAint

ESEint<=>ESAEAint : Internal Dimer ATP Binding 2
vf=katpon*ESEint*ATPconc
vr=katpoff*ESAEAint

ESESint<=>ESAESAint : Internal Dimer ATP Binding 3
vf=katpon*ESESint*ATPconc
vr=katpoff*ESAESAint

EPEPint<=>EAPEAPint : Internal Dimer ATP Binding 4
vf=katpon*EPEPint*ATPconc
vr=katpoff*EAPEAPint

ESPEPint<=>ESAPEAPint : Internal Dimer ATP Binding 5
vf=katpon*ESPEPint*ATPconc
vr=katpoff*ESAPEAPint

ESPESPint<=>ESAPESAPint : Internal Dimer ATP Binding 6
vf=katpon*ESPESPint*ATPconc
vr=katpoff*ESAPESAPint

```
EPEPadptint<=>EAPEAPadptint : Internal Dimer ATP Binding 7
        vf=katpon*EPEPadptint*ATPconc
        vr=katpoff*EAPEAPadptint

ESPEPadptint<=>ESAPEAPadptint : Internal Dimer ATP Binding 8
        vf=katpon*ESPEPadptint*ATPconc
        vr=katpoff*ESAPEAPadptint

ESPESPadptint<=>ESAPESAPadptint : Internal Dimer ATP Binding 9
        vf=katpon*ESPESPadptint*ATPconc
        vr=katpoff*ESAPESAPadptint

%DIMER INH BINDING IN THE ENDOSOME

EEint<=>EIEIint : Internal Dimer INH Binding 1
        vf=kinhon*EEint*INHconc
        vr=kinhoff*EIEIint

ESEint<=>ESIEIint : Internal Dimer INH Binding 2
        vf=kinhon*ESEint*INHconc
        vr=kinhoff*ESIEIint

ESESint<=>ESIESIint : Internal Dimer INH Binding 3
        vf=kinhon*ESESint*INHconc
        vr=kinhoff*ESIESIint

EPEPint<=>EIPEIPint : Internal Dimer INH Binding 4
        vf=kinhon*EPEPint*INHconc
        vr=kinhoff*EIPEIPint

ESPEPint<=>ESIPEIPint : Internal Dimer INH Binding 5
        vf=kinhon*ESPEPint*INHconc
        vr=kinhoff*ESIPEIPint

ESPESPint<=>ESIPESIPint : Internal Dimer INH Binding 6
        vf=kinhon*ESPESPint*INHconc
        vr=kinhoff*ESIPESIPint

EPEPadptint<=>EIPEIPadptint : Internal Dimer INH Binding 7
        vf=kinhon*EPEPadptint*INHconc
        vr=kinhoff*EIPEIPadptint

ESPEPadptint<=>ESIPEIPadptint : Internal Dimer INH Binding 8
        vf=kinhon*ESPEPadptint*INHconc
        vr=kinhoff*ESIPEIPadptint

ESPESPadptint<=>ESIPESIPadptint : Internal Dimer INH Binding 9
        vf=kinhon*ESPESPadptint*INHconc
        vr=kinhoff*ESIPESIPadptint

%DIMER EGF BINDING IN THE ENDOSOME
```

EEint+Sint<=>ESEint : Internal Dimer EGF Binding 1
vf=2*kegfonint*Sint*EEint
vr=kegfoffint*ESEint

ESEint+Sint<=>ESESint : Internal Dimer EGF Binding 2
vf=kegfonint*Sint*ESEint
vr=kegfoffint*ESESint

EAEAint+Sint<=>ESAEAint : Internal Dimer EGF Binding 3
vf=2*kegfonint*Sint*EAEAint
vr=kegfoffint*ESAEAint

ESAEAint+Sint<=>ESAESAint : Internal Dimer EGF Binding 4
vf=kegfonint*Sint*ESAEAint
vr=kegfoffint*ESAESAint

EIEIint+Sint<=>ESIEIint : Internal Dimer EGF Binding 5
vf=2*kegfonint*Sint*EIEIint
vr=kegfoffint*ESIEIint

ESIEIint+Sint<=>ESIESIint : Internal Dimer EGF Binding 6
vf=kegfonint*Sint*ESIEIint
vr=kegfoffint*ESIESIint

EPEPint+Sint<=>ESPEPint : Internal Dimer EGF Binding 7
vf=2*kegfonint*Sint*EPEPint
vr=kegfoffint*ESPEPint

ESPEPint+Sint<=>ESPESPint : Internal Dimer EGF Binding 8
vf=kegfonint*Sint*ESPEPint
vr=kegfoffint*ESPESPint

EAPEAPint+Sint<=>ESAPEAPint : Internal Dimer EGF Binding 9
vf=2*kegfonint*Sint*EAPEAPint
vr=kegfoffint*ESAPEAPint

ESAPEAPint+Sint<=>ESAPESAPint : Internal Dimer EGF Binding 10
vf=kegfonint*Sint*ESAPEAPint
vr=kegfoffint*ESAPESAPint

EIPEIPint+Sint<=>ESIPEIPint : Internal Dimer EGF Binding 11
vf=2*kegfonint*Sint*EIPEIPint
vr=kegfoffint*ESIPEIPint

ESIPEIPint+Sint<=>ESIPESIPint : Internal Dimer EGF Binding 12
vf=kegfonint*Sint*ESIPEIPint
vr=kegfoffint*ESIPESIPint

EPEPadptint+Sint<=>ESPEPadptint : Internal Dimer EGF Binding 13
vf=2*kegfonint*Sint*EPEPadptint

vr=kegfoffint*ESPEPadptint

ESPEPadptint+Sint<=>ESPESPadptint : Internal Dimer EGF Binding 14
vf=kegfonint*Sint*ESPEPadptint
vr=kegfoffint*ESPESPadptint

EAPEAPadptint+Sint<=>ESAPEAPadptint : Internal Dimer EGF Binding 15
vf=2*kegfonint*Sint*EAPEAPadptint
vr=kegfoffint*ESAPEAPadptint

ESAPEAPadptint+Sint<=>ESAPESAPadptint : Internal Dimer EGF Binding 16
vf=kegfonint*Sint*ESAPEAPadptint
vr=kegfoffint*ESAPESAPadptint

EIPEIPadptint+Sint<=>ESIPEIPadptint : Internal Dimer EGF Binding 17
vf=2*kegfonint*Sint*EIPEIPadptint
vr=kegfoffint*ESIPEIPadptint

ESIPEIPadptint+Sint<=>ESIPESIPadptint : Internal Dimer EGF Binding 18
vf=kegfonint*Sint*ESIPEIPadptint
vr=kegfoffint*ESIPESIPadptint

%PHOSPHORYLATION IN THE ENDOSOME

EAEAint=>EPEPint : Internal Phosphorylation 1
vf=kcatNOEGF*EAEAint

ESAEAint=>ESPEPint : Internal Phosphorylation 2
vf=kcatEGF*ESAEAint

ESAESAint=>ESPESPint : Internal Phosphorylation 3
vf=kcatEGF*ESAESAint

%DEPHOSPHORYLATION IN THE ENDOSOME

EPint=>Eint : Internal Dephosphorylation 1
vf=kdephosINT*EPint

EAPint=>EAint : Internal Dephosphorylation 2
vf=kdephosINT*EAPint

EIPint=>EIint : Internal Dephosphorylation 3
vf=kdephosINT*EIPint

ESPint=>ESint : Internal Dephosphorylation 4
vf=kdephosINT*ESPint

ESAPint=>ESAint : Internal Dephosphorylation 5
vf=kdephosINT*ESAPint

ESIPint=>ESIint : Internal Dephosphorylation 6

vf=kdephosINT*ESIPint

EPEPint=>EEint : Internal Dephosphorylation 7
vf=kdephosINT*EPEPint

EAPEAPint=>EAEAint : Internal Dephosphorylation 8
vf=kdephosINT*EAPEAPint

EIPEIPint=>EIEIint : Internal Dephosphorylation 9
vf=kdephosINT*EIPEIPint

ESPEPint=>ESEint : Internal Dephosphorylation 10
vf=kdephosINT*ESPEPint

ESAPEAPint=>ESAEAint : Internal Dephosphorylation 11
vf=kdephosINT*ESAPEAPint

ESIPEIPint=>ESIEIint : Internal Dephosphorylation 12
vf=kdephosINT*ESIPEIPint

ESPESPint=>ESESint : Internal Dephosphorylation 13
vf=kdephosINT*ESPESPint

ESAPESAPint=>ESAESAint : Internal Dephosphorylation 14
vf=kdephosINT*ESAPESAPint

ESIPESIPint=>ESIESIint : Internal Dephosphorylation 15
vf=kdephosINT*ESIPESIPint

EPcetint=>Ecetint : Internal Dephosphorylation 16
vf=kdephosINT*EPcetint

EAPcetint=>EAcetint : Internal Dephosphorylation 17
vf=kdephosINT*EAPcetint

EIPcetint=>EIcetint : Internal Dephosphorylation 18
vf=kdephosINT*EIPcetint

%ADAPTER BINDING IN THE CELL INTERIOR

EPint+adpt<=>EPadptint : Internal Adapter Binding 1
vf=kadpton*EPint*adpt
vr=kadptoff*EPadptint

EAPint+adpt<=>EAPadptint : Internal Adapter Binding 2
vf=kadpton*EAPint*adpt
vr=kadptoff*EAPadptint

EIPint+adpt<=>EIPadptint : Internal Adapter Binding 3
vf=kadpton*EIPint*adpt
vr=kadptoff*EIPadptint

ESPint+adpt<=>ESPadptint : Internal Adapter Binding 4
vf=kadpton*ESPint*adpt
vr=kadptoff*ESPadptint

ESAPint+adpt<=>ESAPadptint : Internal Adapter Binding 5
vf=kadpton*ESAPint*adpt
vr=kadptoff*ESAPadptint

ESIPint+adpt<=>ESIPadptint : Internal Adapter Binding 6
vf=kadpton*ESIPint*adpt
vr=kadptoff*ESIPadptint

EPEPint+2*adpt<=>EPEPadptint : Internal Adapter Binding 7
vf=kadpton*EPEPint*adpt
vr=kadptoff*EPEPadptint

EAPEAPint+2*adpt<=>EAPEAPadptint : Internal Adapter Binding 8
vf=kadpton*EAPEAPint*adpt
vr=kadptoff*EAPEAPadptint

EIPEIPint+2*adpt<=>EIPEIPadptint : Internal Adapter Binding 9
vf=kadpton*EIPEIPint*adpt
vr=kadptoff*EIPEIPadptint

ESPEPint+2*adpt<=>ESPEPadptint : Internal Adapter Binding 10
vf=kadpton*ESPEPint*adpt
vr=kadptoff*ESPEPadptint

ESAPEAPint+2*adpt<=>ESAPEAPadptint : Internal Adapter Binding 11
vf=kadpton*ESAPEAPint*adpt
vr=kadptoff*ESAPEAPadptint

ESIPEIPint+2*adpt<=>ESIPEIPadptint : Internal Adapter Binding 12
vf=kadpton*ESIPEIPint*adpt
vr=kadptoff*ESIPEIPadptint

ESPESPint+2*adpt<=>ESPESPadptint : Internal Adapter Binding 13
vf=kadpton*ESPESPint*adpt
vr=kadptoff*ESPESPadptint

ESAPESAPint+2*adpt<=>ESAPESAPadptint : Internal Adapter Binding 14
vf=kadpton*ESAPESAPint*adpt
vr=kadptoff*ESAPESAPadptint

ESIPESIPint+2*adpt<=>ESIPESIPadptint : Internal Adapter Binding 15
vf=kadpton*ESIPESIPint*adpt
vr=kadptoff*ESIPESIPadptint

EPcetint+adpt<=>EPcetadptint : Internal Adapter Binding 16
vf=kadpton*EPcetint*adpt

vr=kadptoff*EPcetadptint

EAPcetint+adpt<=>EAPcetadptint : Internal Adapter Binding 17
vf=kadpton*EAPcetint*adpt
vr=kadptoff*EAPcetadptint

EIPcetint+adpt<=>EIPcetadptint : Internal Adapter Binding 18
vf=kadpton*EIPcetint*adpt
vr=kadptoff*EIPcetadptint

%UNOCCUPIED DEGRADATION

Eint=>debris : Unoccupied Degradation 1
vf=kexit*(1-frecunoc)*Eint

EAint=>debris : Unoccupied Degradation 2
vf=kexit*(1-frecunoc)*EAint

EIint=>debris : Unoccupied Degradation 3
vf=kexit*(1-frecunoc)*EIint

EPint=>debris : Unoccupied Degradation 4
vf=kexit*(1-frecunoc)*EPint

EAPint=>debris : Unoccupied Degradation 5
vf=kexit*(1-frecunoc)*EAPint

EIPint=>debris : Unoccupied Degradation 6
vf=kexit*(1-frecunoc)*EIPint

EEint=>debris : Unoccupied Degradation 7
vf=kexit*(1-frecunoc)*EEint

EAEAint=>debris : Unoccupied Degradation 8
vf=kexit*(1-frecunoc)*EAEAint

EIEIint=>debris : Unoccupied Degradation 9
vf=kexit*(1-frecunoc)*EIEIint

EPEPint=>debris : Unoccupied Degradation 10
vf=kexit*(1-frecunoc)*EPEPint

EAPEAPint=>debris : Unoccupied Degradation 11
vf=kexit*(1-frecunoc)*EAPEAPint

EIPEIPint=>debris : Unoccupied Degradation 12
vf=kexit*(1-frecunoc)*EIPEIPint

EPadptint=>adpt+debris : Unoccupied Degradation 13
vf=kexit*(1-frecunoc)*EPadptint

EAPadptint=>adpt+debris : Unoccupied Degradation 14
vf=kexit*(1-frecunoc)*EAPadptint

EIPadptint=>adpt+debris : Unoccupied Degradation 15
vf=kexit*(1-frecunoc)*EIPadptint

EPEPadptint=>2*adpt+debris : Unoccupied Degradation 16
vf=kexit*(1-frecunoc)*EPEPadptint

EAPEAPadptint=>2*adpt+debris : Unoccupied Degradation 17
vf=kexit*(1-frecunoc)*EAPEAPadptint

EIPEIPadptint=>2*adpt+debris : Unoccupied Degradation 18
vf=kexit*(1-frecunoc)*EIPEIPadptint

Ecetint=>debrisCET : Unoccupied Degradation 19
vf=kexit*(1-frecunoc)*Ecetint

EAcetint=>debrisCET : Unoccupied Degradation 20
vf=kexit*(1-frecunoc)*EAcetint

EIcetint=>debrisCET : Unoccupied Degradation 21
vf=kexit*(1-frecunoc)*EIcetint

EPcetint=>debrisCET : Unoccupied Degradation 22
vf=kexit*(1-frecunoc)*EPcetint

EAPcetint=>debrisCET : Unoccupied Degradation 23
vf=kexit*(1-frecunoc)*EAPcetint

EIPcetint=>debrisCET : Unoccupied Degradation 24
vf=kexit*(1-frecunoc)*EIPcetint

EPcetadptint=>adpt+debrisCET : Unoccupied Degradation 25
vf=kexit*(1-frecunoc)*EPcetadptint

EAPcetadptint=>adpt+debrisCET : Unoccupied Degradation 26
vf=kexit*(1-frecunoc)*EAPcetadptint

EIPcetadptint=>adpt+debrisCET : Unoccupied Degradation 27
vf=kexit*(1-frecunoc)*EIPcetadptint

%HALF-OCCUPIED DEGRADATION

ESEint=>debrisEGF : Half Occupied Degradation 1
vf=kexit*(1-frecoc)*ESEint

ESAEAint=>debrisEGF : Half Occupied Degradation 2
vf=kexit*(1-frecoc)*ESAEAint

ESIEIint=>debrisEGF : Half Occupied Degradation 3

vf=kexit*(1-frecoc)*ESIEIint

ESPEPint=>debrisEGF : Half Occupied Degradation 4
vf=kexit*(1-frecoc)*ESPEPint

ESAPEAPint=>debrisEGF : Half Occupied Degradation 5
vf=kexit*(1-frecoc)*ESAPEAPint

ESIPEIPint=>debrisEGF : Half Occupied Degradation 6
vf=kexit*(1-frecoc)*ESIPEIPint

ESPEPadptint=>2*adpt+debrisEGF : Half Occupied Degradation 7
vf=kexit*(1-frecoc)*ESPEPadptint

ESAPEAPadptint=>2*adpt+debrisEGF : Half Occupied Degradation 8
vf=kexit*(1-frecoc)*ESAPEAPadptint

ESIPEIPadptint=>2*adpt+debrisEGF : Half Occupied Degradation 9
vf=kexit*(1-frecoc)*ESIPEIPadptint

%OCCUPIED DEGRADATION

ESint=>debrisEGF : Occupied Degradation 1
vf=kexit*(1-frecoc)*ESint

ESAint=>debrisEGF : Occupied Degradation 2
vf=kexit*(1-frecoc)*ESAint

ESIint=>debrisEGF : Occupied Degradation 3
vf=kexit*(1-frecoc)*ESIint

ESPint=>debrisEGF : Occupied Degradation 4
vf=kexit*(1-frecoc)*ESPint

ESAPint=>debrisEGF : Occupied Degradation 5
vf=kexit*(1-frecoc)*ESAPint

ESIPint=>debrisEGF : Occupied Degradation 6
vf=kexit*(1-frecoc)*ESIPint

ESESint=>2*debrisEGF : Occupied Degradation 7
vf=kexit*(1-frecoc)*ESESint

ESAESAint=>2*debrisEGF : Occupied Degradation 8
vf=kexit*(1-frecoc)*ESAESAint

ESIESIint=>2*debrisEGF : Occupied Degradation 9
vf=kexit*(1-frecoc)*ESIESIint

ESPESPint=>2*debrisEGF : Occupied Degradation 10
vf=kexit*(1-frecoc)*ESPESPint

ESAPESAPint=>2*debrisEGF : Occupied Degradation 11
vf=kexit*(1-frecoc)*ESAPESAPint

ESIPESIPint=>2*debrisEGF : Occupied Degradation 12
vf=kexit*(1-frecoc)*ESIPESIPint

ESPadptint=>adpt+debrisEGF : Occupied Degradation 13
vf=kexit*(1-frecoc)*ESPadptint

ESAPadptint=>adpt+debrisEGF : Occupied Degradation 14
vf=kexit*(1-frecoc)*ESAPadptint

ESIPadptint=>adpt+debrisEGF : Occupied Degradation 15
vf=kexit*(1-frecoc)*ESIPadptint

ESPESPadptint=>2*adpt+2*debrisEGF : Occupied Degradation 16
vf=kexit*(1-frecoc)*ESPESPadptint

ESAPESAPadptint=>2*adpt+2*debrisEGF : Occupied Degradation 17
vf=kexit*(1-frecoc)*ESAPESAPadptint

ESIPESIPadptint=>2*adpt+2*debrisEGF : Occupied Degradation 18
vf=kexit*(1-frecoc)*ESIPESIPadptint

%UNOCCUPIED RECYCLE

Eint=>E : Unoccupied Recycle 1
vf=kexit*frecunoc*Eint

EAint=>EA : Unoccupied Recycle 2
vf=kexit*frecunoc*EAint

EIint=>EI : Unoccupied Recycle 3
vf=kexit*frecunoc*EIint

EPint=>EP : Unoccupied Recycle 4
vf=kexit*frecunoc*EPint

EAPint=>EAP : Unoccupied Recycle 5
vf=kexit*frecunoc*EAPint

EIPint=>EIP : Unoccupied Recycle 6
vf=kexit*frecunoc*EIPint

EEint=>EE : Unoccupied Recycle 7
vf=kexit*frecunoc*EEint

EAEAint=>EAEA : Unoccupied Recycle 8
vf=kexit*frecunoc*EAEAint

EIEIint=>EIEI : Unoccupied Recycle 9
vf=kexit*frecunoc*EIEIint

EPEPint=>EPEP : Unoccupied Recycle 10
vf=kexit*frecunoc*EPEPint

EAPEAPint=>EAPEAP : Unoccupied Recycle 11
vf=kexit*frecunoc*EAPEAPint

EIPEIPint=>EIPEIP : Unoccupied Recycle 12
vf=kexit*frecunoc*EIPEIPint

EPadptint=>EPadpt : Unoccupied Recycle 13
vf=kexit*frecunoc*EPadptint

EAPadptint=>EAPadpt : Unoccupied Recycle 14
vf=kexit*frecunoc*EAPadptint

EIPadptint=>EIPadpt : Unoccupied Recycle 15
vf=kexit*frecunoc*EIPadptint

EPEPadptint=>EPEPadpt : Unoccupied Recycle 16
vf=kexit*frecunoc*EPEPadptint

EAPEAPadptint=>EAPEAPadpt : Unoccupied Recycle 17
vf=kexit*frecunoc*EAPEAPadptint

EIPEIPadptint=>EIPEIPadpt : Unoccupied Recycle 18
vf=kexit*frecunoc*EIPEIPadptint

Ecetint=>Ecet : Unoccupied Recycle 19
vf=kexit*frecunoc*Eint

EAcetint=>EAcet : Unoccupied Recycle 20
vf=kexit*frecunoc*EAcetint

EIcetint=>EIcet : Unoccupied Recycle 21
vf=kexit*frecunoc*EIcetint

EPcetint=>EPcet : Unoccupied Recycle 22
vf=kexit*frecunoc*EPcetint

EAPcetint=>EAPcet : Unoccupied Recycle 23
vf=kexit*frecunoc*EAPcetint

EIPcetint=>EIPcet : Unoccupied Recycle 24
vf=kexit*frecunoc*EIPcetint

EPcetadptint=>EPcetadpt : Unoccupied Recycle 25
vf=kexit*frecunoc*EPcetadptint

EAPcetadptint=>EAPcetadpt : Unoccupied Recycle 26
vf=kexit*frecunoc*EAPcetadptint

EIPcetadptint=>EIPcetadpt : Unoccupied Recycle 27
vf=kexit*frecunoc*EIPcetadptint

%HALF-OCCUPIED RECYCLE

ESEint=>ESE : Half Occupied Recycle 1
vf=kexit*frecoc*ESEint

ESAEAint=>ESAEA : Half Occupied Recycle 2
vf=kexit*frecoc*ESAEAint

ESIEIint=>ESIEI : Half Occupied Recycle 3
vf=kexit*frecoc*ESIEIint

ESPEPint=>ESPEP : Half Occupied Recycle 4
vf=kexit*frecoc*ESPEPint

ESAPEAPint=>ESAPEAP : Half Occupied Recycle 5
vf=kexit*frecoc*ESAPEAPint

ESIPEIPint=>ESIPEIP : Half Occupied Recycle 6
vf=kexit*frecoc*ESIPEIPint

ESPEPadptint=>ESPEPadpt : Half Occupied Recycle 7
vf=kexit*frecoc*ESPEPadptint

ESAPEAPadptint=>ESAPEAPadpt : Half Occupied Recycle 8
vf=kexit*frecoc*ESAPEAPadptint

ESIPEIPadptint=>ESIPEIPadpt : Half Occupied Recycle 9
vf=kexit*frecoc*ESIPEIPadptint

%OCCUPIED RECYCLE

ESint=>ES : Occupied Recycle 1
vf=kexit*frecoc*ESint

ESAint=>ESA : Occupied Recycle 2
vf=kexit*frecoc*ESAint

ESIint=>ESI : Occupied Recycle 3
vf=kexit*frecoc*ESIint

ESPint=>ESP : Occupied Recycle 4
vf=kexit*frecoc*ESPint

ESAPint=>ESAP : Occupied Recycle 5
vf=kexit*frecoc*ESAPint

ESIPint=>ESIP : Occupied Recycle 6
vf=kexit*frecoc*ESIPint

ESESint=>ESES : Occupied Recycle 7
vf=kexit*frecoc*ESESint

ESAESAint=>ESAESA : Occupied Recycle 8
vf=kexit*frecoc*ESAESAint

ESIESIint=>ESIESI : Occupied Recycle 9
vf=kexit*frecoc*ESIESIint

ESPESPint=>ESPESP : Occupied Recycle 10
vf=kexit*frecoc*ESPESPint

ESAPESAPint=>ESAPESAP : Occupied Recycle 11
vf=kexit*frecoc*ESAPESAPint

ESIPESIPint=>ESIPESIP : Occupied Recycle 12
vf=kexit*frecoc*ESIPESIPint

ESPadptint=>ESPadpt : Occupied Recycle 13
vf=kexit*frecoc*ESPadptint

ESAPadptint=>ESAPadpt : Occupied Recycle 14
vf=kexit*frecoc*ESAPadptint

ESIPadptint=>ESIPadpt : Occupied Recycle 15
vf=kexit*frecoc*ESIPadptint

ESPESPadptint=>ESPESPadpt : Occupied Recycle 16
vf=kexit*frecoc*ESPESPadptint

ESAPESAPadptint=>ESAPESAPadpt : Occupied Recycle 17
vf=kexit*frecoc*ESAPESAPadptint

ESIPESIPadptint=>ESIPESIPadpt : Occupied Recycle 18
vf=kexit*frecoc*ESIPESIPadptint

********** MODEL FUNCTIONS

********** MODEL EVENTS

********** MODEL MATLAB FUNCTIONS