

In[314]:=

```

useSwitchA = False; (* Change this to change from low-
hystereis switch (A) to high-hysteresis swith (B). False means switch B *)

NormFactor = 70;
foldChange = .
h = 4;
hR = 1;
s = If[useSwitchA, 1.3, 2.0]; (* 1.3 or 2.0 *)
kdeg = 0.07; (* was 0.07 *)
VmE = 15 / NormFactor;
KmE = 70 / NormFactor;
KdT = 50 / NormFactor;
VmT = 15 / NormFactor; (* switch to >15 to make foldChange=1 favor TFGb3 *)
KmT = 70 / NormFactor; (* switch to 90 to make foldChange=1 favor TGFb3 *)
KdE = 50 / NormFactor;
RE = Round[(4^(1/h)) * KmE * NormFactor * s, 10] * foldChange / NormFactor
RT = Round[(4^(1/h)) * KmT * NormFactor * s * If[useSwitchA, 1.2, 1.0], 10] / NormFactor
(* 1.0 or 1.2 *)

```

Out[322]=
$$\frac{20 \text{ foldChange}}{7}$$

Out[323]=
$$\frac{20}{7}$$

```

In[324]:= vEform = VmE * (KmE^h) / (KmE^h + ((RT / (1 + KdT / TGF))^h))
vTform = VmT * (KmT^h) / (KmT^h + ((RE / (1 + KdE / EGF))^h))
vEdeg = kdeg * EGF
vTdeg = kdeg * TGF

```

Out[324]=
$$\frac{3}{14 \left(1 + \frac{160000}{2401 \left(1 + \frac{5}{7 \text{TGF}} \right)^4} \right)}$$

Out[325]=
$$\frac{3}{14 \left(1 + \frac{160000 \text{ foldChange}^4}{2401 \left(1 + \frac{5}{7 \text{EGF}} \right)^4} \right)}$$

Out[326]= 0.07 EGF

Out[327]= 0.07 TGF

```

In[328]:= NSolve[{vEform == vEdeg, (vTform /. foldChange -> 0.8) == vTdeg},
{EGF, TGF}, Reals, Method -> "EndomorphismMatrix"]
NSolve[{vEform == vEdeg, (vTform /. foldChange -> 0.8) == vTdeg}, {EGF, TGF}, Reals]

```

Out[328]= {{EGF -> 0.103245, TGF -> 3.04012}}

Out[329]= {}

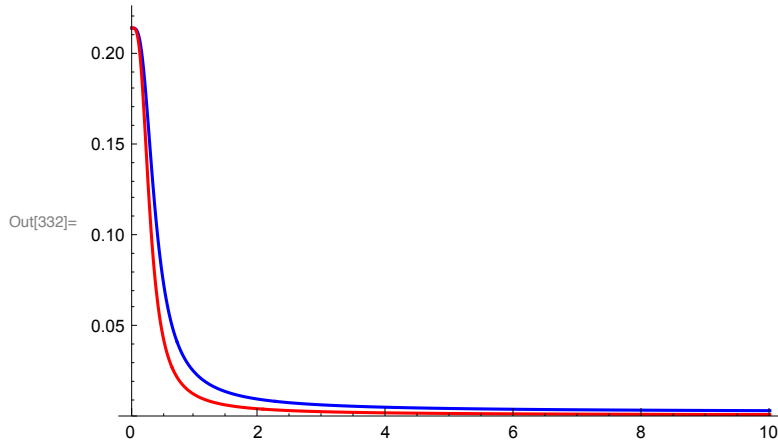
```

In[330]:= testValue = 1.2
Limit[vTform /. foldChange → testValue, EGF → Infinity]
Show[
  Plot[vEform /. foldChange → testValue,
    {TGF, 0, 10}, PlotRange → {All, {0, All}}, PlotStyle → Blue],
  Plot[vTform /. foldChange → testValue, {EGF, 0, 10},
    PlotRange → {All, {0, All}}, PlotStyle → Red]]

```

Out[330]= 1.2

Out[331]= 0.0015396



```

In[333]:= testFC = 0.8
NSolve[{vEform == vEdeg, (vTform /. foldChange → testFC) == vTdeg},
  {EGF, TGF}, Reals, Method → "EndomorphismMatrix"]

```

Out[333]= 0.8

Out[334]= {{EGF → 0.103245, TGF → 3.04012}}

```

In[335]:= steadyStateSolutionsAsReplacements =
  Table[{foldChange, NSolve[{vEform == vEdeg, vTform == vTdeg}, {EGF, TGF},
    Reals, Method → "EndomorphismMatrix"]], {foldChange, 0.25, 2.0, 0.01]]

```

Out[335]= {{0.25, {{EGF → 0.102727, TGF → 3.06103}}}, {0.26, {{EGF → 0.102728, TGF → 3.06099}}}, {0.27, {{EGF → 0.102729, TGF → 3.06095}}}, {0.28, {{EGF → 0.10273, TGF → 3.06091}}}, {0.29, {{EGF → 0.102731, TGF → 3.06086}}}, {0.3, {{EGF → 0.102733, TGF → 3.06081}}}, {0.31, {{EGF → 0.102734, TGF → 3.06075}}}, {0.32, {{EGF → 0.102736, TGF → 3.06069}}}, {0.33, {{EGF → 0.102737, TGF → 3.06062}}}, {0.34, {{EGF → 0.102739, TGF → 3.06054}}}, {0.35, {{EGF → 0.102741, TGF → 3.06046}}}, {0.36, {{EGF → 0.102744, TGF → 3.06037}}}, {0.37, {{EGF → 0.102746, TGF → 3.06027}}}, {0.38, {{EGF → 0.102749, TGF → 3.06016}}}, {0.39, {{EGF → 0.102752, TGF → 3.06004}}}, {0.4, {{EGF → 0.102755, TGF → 3.05992}}}, {0.41, {{EGF → 0.102758, TGF → 3.05978}}}, {0.42, {{EGF → 0.102762, TGF → 3.05964}}}, {0.43, {{EGF → 0.102765, TGF → 3.05948}}}, {0.44, {{EGF → 0.10277, TGF → 3.05931}}}, {0.45, {{EGF → 0.102774, TGF → 3.05913}}}, {0.46, {{EGF → 0.102779, TGF → 3.05894}}}, {0.47, {{EGF → 0.102784, TGF → 3.05873}}}, {0.48, {{EGF → 0.102789, TGF → 3.05851}}}, {0.49, {{EGF → 0.102795, TGF → 3.05828}}}, {0.5, {{EGF → 0.102801, TGF → 3.05803}}}, {0.51, {{EGF → 0.102807, TGF → 3.05777}}}, {0.52, {{EGF → 0.102814, TGF → 3.05749}}}, {0.53, {{EGF → 0.102822, TGF → 3.05719}}}, {0.54, {{EGF → 0.102829, TGF → 3.05688}}}, {0.55, {{EGF → 0.102838, TGF → 3.05655}}}, {0.56, {{EGF → 0.102846, TGF → 3.0562}}}, {0.57, {{EGF → 0.102855, TGF → 3.05583}}}, {0.58, {{EGF → 0.102865, TGF → 3.05544}}}, {0.59, {{EGF → 0.102875, TGF → 3.05503}}},

{0.6, {{EGF → 0.102886, TGF → 3.0546}}}, {0.61, {{EGF → 0.102897, TGF → 3.05414}}},
 {0.62, {{EGF → 0.102909, TGF → 3.05366}}}, {0.63, {{EGF → 0.102921, TGF → 3.05316}}},
 {0.64, {{EGF → 0.102934, TGF → 3.05263}}}, {0.65, {{EGF → 0.102948, TGF → 3.05208}}},
 {0.66, {{EGF → 0.102962, TGF → 3.0515}}}, {0.67, {{EGF → 0.102977, TGF → 3.0509}}},
 {0.68, {{EGF → 0.102993, TGF → 3.05026}}}, {0.69, {{EGF → 0.103009, TGF → 3.0496}}},
 {0.7, {{EGF → 0.103026, TGF → 3.04891}}}, {0.71, {{EGF → 0.103044, TGF → 3.04818}}},
 {0.72, {{EGF → 0.103063, TGF → 3.04743}}}, {0.73, {{EGF → 0.103083, TGF → 3.04664}}},
 {0.74, {{EGF → 0.103103, TGF → 3.04582}}}, {0.75, {{EGF → 0.103124, TGF → 3.04496}}},
 {0.76, {{EGF → 0.103147, TGF → 3.04407}}}, {0.77, {{EGF → 0.10317, TGF → 3.04314}}},
 {0.78, {{EGF → 0.103194, TGF → 3.04217}}}, {0.79, {{EGF → 0.103219, TGF → 3.04116}}},
 {0.8, {{EGF → 0.103245, TGF → 3.04012}}}, {0.81, {{EGF → 0.103272, TGF → 3.03903}}},
 {0.82, {{EGF → 0.103301, TGF → 3.0379}}}, {0.83, {{EGF → 2.24098, TGF → 0.267193}},
 {EGF → 0.10333, TGF → 3.03673}, {EGF → 1.61019, TGF → 0.369626}}},
 {0.84, {{EGF → 2.42245, TGF → 0.239122}, {EGF → 0.10336, TGF → 3.03551},
 {EGF → 1.43017, TGF → 0.404743}}}, {0.85, {{EGF → 2.54037, TGF → 0.220052},
 {EGF → 0.103392, TGF → 3.03424}, {EGF → 1.31037, TGF → 0.430951}}},
 {0.86, {{EGF → 2.62823, TGF → 0.204981}, {EGF → 0.103425, TGF → 3.03293},
 {EGF → 1.21789, TGF → 0.45325}}}, {0.87, {{EGF → 2.69724, TGF → 0.192321},
 {EGF → 0.103459, TGF → 3.03157}, {EGF → 1.142, TGF → 0.473229}}},
 {0.88, {{EGF → 2.753, TGF → 0.181323}, {EGF → 0.103495, TGF → 3.03016},
 {EGF → 1.07755, TGF → 0.491638}}}, {0.89, {{EGF → 2.79883, TGF → 0.171563},
 {EGF → 0.103532, TGF → 3.0287}, {EGF → 1.02156, TGF → 0.508903}}},
 {0.9, {{EGF → 2.83695, TGF → 0.162772}, {EGF → 0.10357, TGF → 3.02719},
 {EGF → 0.972133, TGF → 0.52529}}}, {0.91, {{EGF → 2.86892, TGF → 0.154769},
 {EGF → 0.103609, TGF → 3.02562}, {EGF → 0.927962, TGF → 0.540982}}},
 {0.92, {{EGF → 2.8959, TGF → 0.147423}, {EGF → 0.10365, TGF → 3.024},
 {EGF → 0.888108, TGF → 0.556111}}}, {0.93, {{EGF → 2.91879, TGF → 0.140636},
 {EGF → 0.103693, TGF → 3.02232}, {EGF → 0.85187, TGF → 0.570774}}},
 {0.94, {{EGF → 2.93828, TGF → 0.134334}, {EGF → 0.103737, TGF → 3.02058},
 {EGF → 0.818706, TGF → 0.585046}}}, {0.95, {{EGF → 2.95492, TGF → 0.128458},
 {EGF → 0.103783, TGF → 3.01878}, {EGF → 0.788187, TGF → 0.598987}}},
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 {EGF → 0.103982, TGF → 3.01096}, {EGF → 0.686538, TGF → 0.65228}}},
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 {EGF → 0.104093, TGF → 3.00665}, {EGF → 0.645027, TGF → 0.677864}}},
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 {EGF → 0.626072, TGF → 0.690468}}}, {1.03, {{EGF → 3.02653, TGF → 0.0923838},
 {EGF → 0.104211, TGF → 3.00206}, {EGF → 0.608172, TGF → 0.702969}}},
 {1.04, {{EGF → 3.03093, TGF → 0.0888876}, {EGF → 0.104273, TGF → 2.99965},
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 {EGF → 0.104337, TGF → 2.99716}, {EGF → 0.575172, TGF → 0.727716}}},
 {1.06, {{EGF → 3.03806, TGF → 0.0823986}, {EGF → 0.104404, TGF → 2.99459},
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 {EGF → 0.104473, TGF → 2.99195}, {EGF → 0.545409, TGF → 0.752206}}},
 {1.08, {{EGF → 3.04345, TGF → 0.0765103}, {EGF → 0.104544, TGF → 2.98921},
 {EGF → 0.531585, TGF → 0.764381}}}, {1.09, {{EGF → 3.04564, TGF → 0.0737684},
 {EGF → 0.104617, TGF → 2.9864}, {EGF → 0.518396, TGF → 0.776521}}},
 {1.1, {{EGF → 3.04755, TGF → 0.0711507}, {EGF → 0.104693, TGF → 2.98349},
 {EGF → 0.505796, TGF → 0.788636}}}, {1.11, {{EGF → 3.04921, TGF → 0.0686501},
 {EGF → 0.104772, TGF → 2.9805}, {EGF → 0.493744, TGF → 0.800732}}},

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{1.12, {{EGF → 3.05067, TGF → 0.0662599}, {EGF → 0.104853, TGF → 2.97741},
{EGF → 0.482201, TGF → 0.812818}}}, {1.13, {{EGF → 3.05194, TGF → 0.0639739},
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{1.18, {{EGF → 3.05628, TGF → 0.0539231}, {EGF → 0.1054, TGF → 2.95679},
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{EGF → 0.106456, TGF → 2.91804}, {EGF → 0.352717, TGF → 0.997117}}},
{1.28, {{EGF → 3.05974, TGF → 0.0391043}, {EGF → 0.106594, TGF → 2.91306},
{EGF → 0.346177, TGF → 1.00986}}}, {1.29, {{EGF → 3.05991, TGF → 0.0379192},
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{1.32, {{EGF → 3.06029, TGF → 0.0346221}, {EGF → 0.107197, TGF → 2.8916},
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{EGF → 0.109886, TGF → 2.80053}, {EGF → 0.257812, TGF → 1.24573}}},
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{EGF → 0.110435, TGF → 2.78282}, {EGF → 0.249489, TGF → 1.27693}}},
{1.48, {{EGF → 3.06106, TGF → 0.0219952}, {EGF → 0.110727, TGF → 2.7735},

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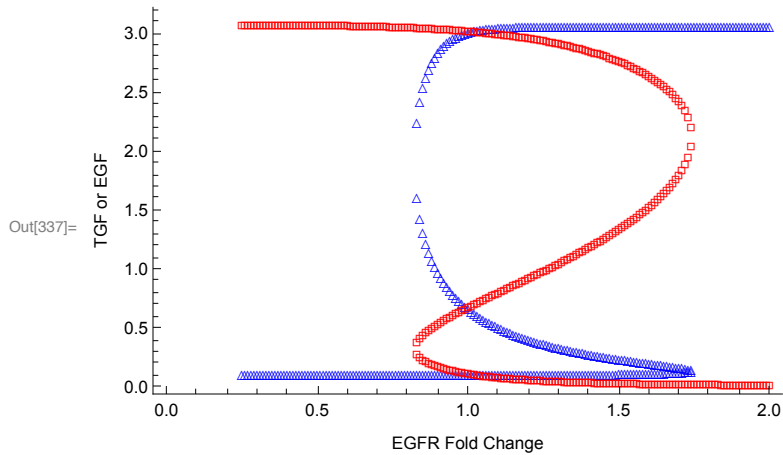
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{EGF → 0.245443, TGF → 1.29292}}}, {1.49, {{EGF → 3.06108, TGF → 0.0214147},
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{1.86, {{EGF → 3.06122, TGF → 0.00885482}}},
{1.87, {{EGF → 3.06122, TGF → 0.00866746}}},
{1.88, {{EGF → 3.06122, TGF → 0.00848502}}},
{1.89, {{EGF → 3.06122, TGF → 0.00830734}}},
{1.9, {{EGF → 3.06122, TGF → 0.00813429}}},
{1.91, {{EGF → 3.06122, TGF → 0.00796571}}},

```

```
{1.92, {{EGF → 3.06122, TGF → 0.00780147}}},
{1.93, {{EGF → 3.06122, TGF → 0.00764143}}},
{1.94, {{EGF → 3.06122, TGF → 0.00748547}}},
{1.95, {{EGF → 3.06122, TGF → 0.00733347}}},
{1.96, {{EGF → 3.06122, TGF → 0.00718529}}},
{1.97, {{EGF → 3.06122, TGF → 0.00704084}}},
{1.98, {{EGF → 3.06122, TGF → 0.00689999}}},
{1.99, {{EGF → 3.06122, TGF → 0.00676265}}},
{2., {{EGF → 3.06122, TGF → 0.00662869}}}
```

```
In[336]:= steadyStateSolutions =
  Flatten[({#[[1]], EGF, TGF} /. #[[2]] & /@ steadyStateSolutionsAsReplacements, 1];
ListPlot[{steadyStateSolutions[[All, {1, 2}]], steadyStateSolutions[[All, {1, 3}]]},
  Joined → False, Frame → {{True, False}, {True, False}},
  FrameLabel → {"EGFR Fold Change", "TGF or EGF"},
  PlotMarkers → {"Δ", "□"}, PlotStyle → {Blue, Red}]
```



```

In[338]:= (* Can we reorder solutions so Joined→True will be effective? *)
sSS1 = RandomChoice[steadyStateSolutions]
Nearest[Complement[steadyStateSolutions, {sSS1}], sSS1][[1]]

orderedSteadyStateSolutions = {steadyStateSolutions[[1]]}
Do[
  sSS1 = orderedSteadyStateSolutions[[-1]];
  nextSolution = Nearest[
    Complement[steadyStateSolutions, orderedSteadyStateSolutions], sSS1][[1]];
  AppendTo[orderedSteadyStateSolutions, nextSolution]
  , {i, 2, Length[steadyStateSolutions]}]

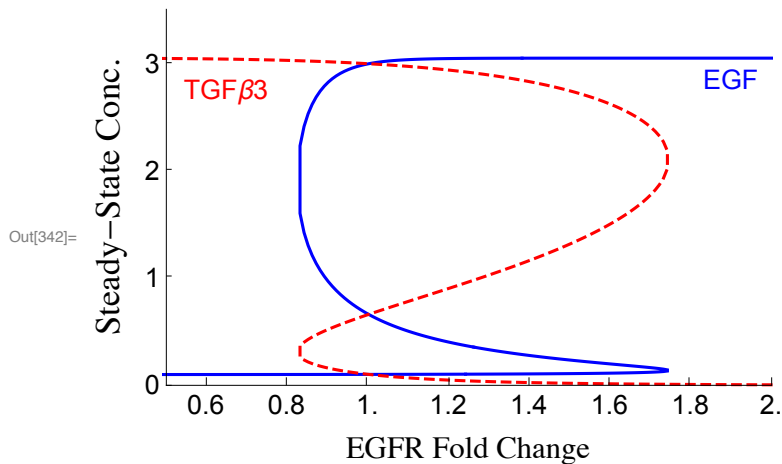
Show[
  ListPlot[{orderedSteadyStateSolutions[[All, {1, 2}]],
    orderedSteadyStateSolutions[[All, {1, 3}]]}, Joined → True,
  Frame → {{True, False}, {True, False}}, FrameLabel →
    {Text[Style["EGFR Fold Change", 16]], Text[Style["Steady-State Conc.", 18]]},
  PlotStyle → {Directive[Blue], Directive[Red, Dashed]},
  PlotRange → {{0.5, 2.0}, {0, 3.5}}, FrameStyle → Directive[14],
  FrameTicks → {{0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0}, {0, 1, 2, 3}},
  Graphics[{
    Text[Style["EGF", Blue, 14], {1.9, 2.85}],
    Text[Style["TGFβ3", Red, 14], {0.65, 2.75}]
  }]]

```

Out[338]= {1.52, 3.06112, 0.0197838}

Out[339]= {1.53, 3.06113, 0.0192748}

Out[340]= {{0.25, 0.102727, 3.06103}}



```

In[343]:= (* Plot so that unstable solution region is the one that is dashed *)
breakPoints = Flatten[Position[Differences[orderedSteadyStateSolutions[[All, 1]]],
  0.]]
orderedSteadyStateSolutions[[breakPoints[[1]] ;; breakPoints[[1]] + 1]]
orderedSteadyStateSolutions[[breakPoints[[2]] ;; breakPoints[[2]] + 1]]

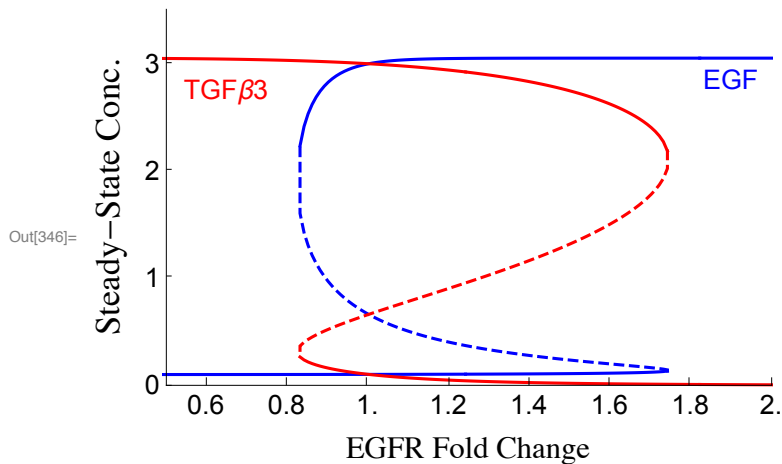
Show[
  ListPlot[
    {orderedSteadyStateSolutions[[ ;; breakPoints[[1]], {1, 2}]],
      orderedSteadyStateSolutions[[breakPoints[[1]] ;; breakPoints[[2]] + 1, {1, 2}]],
      orderedSteadyStateSolutions[[breakPoints[[2]] + 1 ;;, {1, 2}]],
      orderedSteadyStateSolutions[[ ;; breakPoints[[1]], {1, 3}]],
      orderedSteadyStateSolutions[[breakPoints[[1]] ;; breakPoints[[2]] + 1, {1, 3}]],
      orderedSteadyStateSolutions[[breakPoints[[2]] + 1 ;;, {1, 3}]]},
    Joined → True,
    Frame → {{True, False}, {True, False}}, FrameLabel →
      {Text[Style["EGFR Fold Change", 16]], Text[Style["Steady-State Conc.", 18]]},
    PlotStyle → {Directive[Blue], Directive[Blue, Dashed], Directive[Blue],
      Directive[Red], Directive[Red, Dashed], Directive[Red]},
    PlotRange → {{0.5, 2.0}, {0, 3.5}}, FrameStyle → Directive[14],
    FrameTicks → {{0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0}, {0, 1, 2, 3}},
    Graphics[{{
      Text[Style["EGF", Blue, 14], {1.9, 2.85}],
      Text[Style["TGFβ3", Red, 14], {0.65, 2.75}]
    }}]

```

Out[343]= {150, 242}

Out[344]= {{1.74, 0.135621, 2.19278}, {1.74, 0.146171, 2.02906}}

Out[345]= {{0.83, 1.61019, 0.369626}, {0.83, 2.24098, 0.267193}}




```

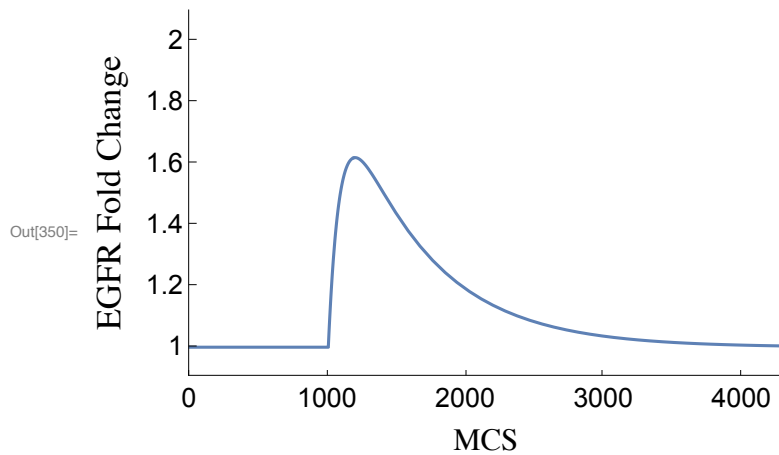
In[347]:= (* form for a transient perturbation of foldChange *)
f = 1 + UnitStep[t - t0] * ΔfMax * (1 - Exp[-(t - t0) / τUp]) * Exp[-(t - t0) / τDown]
tDependenceForFoldChangeSubList =
  {ΔfMax → If[useSwitchA, 1.3, 1.0], t0 → 1000, τUp → 100, τDown → 600}
FindMaximum[f /. tDependenceForFoldChangeSubList, {t, 1100}]
Plot[f /. tDependenceForFoldChangeSubList, {t, 0, 4300},
  PlotRange → {{0, 4300}, {0.9, 2.1}}, Frame → {{True, False}, {True, False}},
  FrameLabel → {Text[Style["MCS", 16]], Text[Style["EGFR Fold Change", 18]]},
  FrameTicks -> {{0, 1000, 2000, 3000, 4000}, {1, 1.2, 1.4, 1.6, 1.8, 2}},
  FrameStyle → Directive[14]]

```

Out[347]= $1 + e^{\frac{-t+t_0}{\tau_{\text{Down}}}} \left(1 - e^{\frac{-t+t_0}{\tau_{\text{Up}}}}\right) \Delta f_{\text{Max}} \text{UnitStep}[t - t_0]$

Out[348]= {ΔfMax → 1., t0 → 1000, τUp → 100, τDown → 600}

Out[349]= {1.61973, {t → 1194.59}}



```

In[351]:= EGF = .
          TGF = .
          (* EGF[0] = .
            TGF[0] = . *)
          tDependentSubList =
            {EGF → EGF[t], TGF → TGF[t], foldChange → f /. tDependenceForFoldChangeSubList}
          EGF'[t] == ((vEform - vEdeg) /. tDependentSubList);
          TGF'[t] == ((vTform - vTdeg) /. tDependentSubList);
          solutions = NDSolve[{
            EGF'[t] == ((vEform - vEdeg) /. tDependentSubList),
            TGF'[t] == ((vTform - vTdeg) /. tDependentSubList),
            EGF[0] == 0.001, TGF[0] == 0.001
          }, {EGF, TGF}, {t, 0, 6000}]
          Plot[{EGF[t] /. solutions[[1]], TGF[t] /. solutions[[1]]}, {t, 0, 6000},
            PlotStyle → {Blue, Red}, Frame → {{True, False}, {True, False}},
            FrameLabel → {"t (mcs)", "TGF (RED) or EGF (BLUE)"}, PlotRange → {All, {0, 3.8}}]

```

```

Out[353]= {EGF → EGF[t], TGF → TGF[t], foldChange → 1 + 1. e $\frac{1000-t}{600}$  (1 - e $\frac{1000-t}{100}$ ) UnitStep[-1000 + t]}

```

```

Out[356]= {{EGF → InterpolatingFunction[
  Domain: {{0., 6.00×103}}
  Output scalar
],
  TGF → InterpolatingFunction[
  Domain: {{0., 6.00×103}}
  Output scalar
]}}

```

