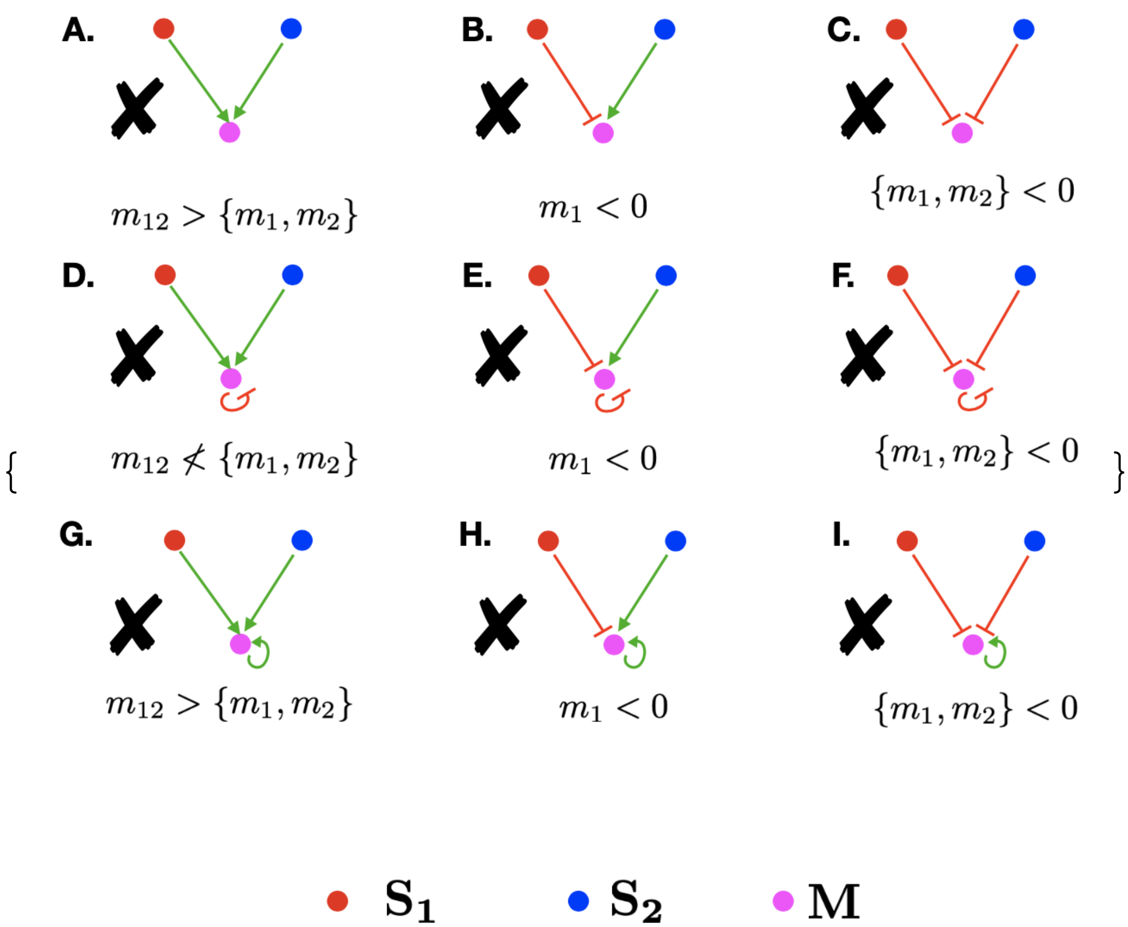
Minimal regulation network for slope antagonism

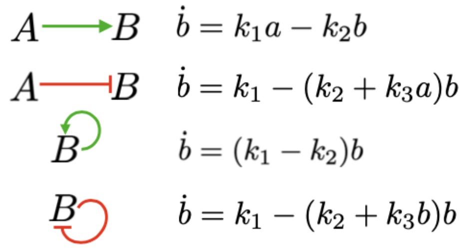
Three node networks

In this section we try to find the minimal regulation network that can explain slope antagonism. For this we first look at all possible three node networks excluding the symmetric cases. We find the following 9 networks-

{}



We analyze each of these nine networks using-



Network A

Equation for the dynamics of M-

In[246]:=
```
dmdt = k_m0 + k_m1 * s_1 + k_m2 * s_2 - k_dm * m;
```

We can solve for m as-

In[247]:=
```
Solve[dmdt == 0, m]
```

Out[247]= $\left\{\left\{m \to \frac{k_{m0} + k_{m1}\, s_1 + k_{m2}\, s_2}{k_{dm}}\right\}\right\}$

Surface map and derivatives of M

We want to check if network A can explain slope antagonism topologically. For that we set all reaction rates to 1, Δs_1 and Δs_2 to 1 and look at the surface maps and derivatives. So for analysis and plots m is-

In[11]:= $mP = \frac{1 + 1 * s_1 + 1 * s_2}{1};$

When only individual signals are present,

In[12]:=
```
mP1 = s_1;
mP2 = s_2;
```

So, we now look at the derivatives,

In[14]:=
```
m_1 = D[mP1, s_1]
```

Out[14]= 1

In[15]:=
```
m_2 = D[mP2, s_2]
```

Out[15]= 1

In[16]:=
```
m_12 = D[mP, s_1] + D[mP, s_2]
```

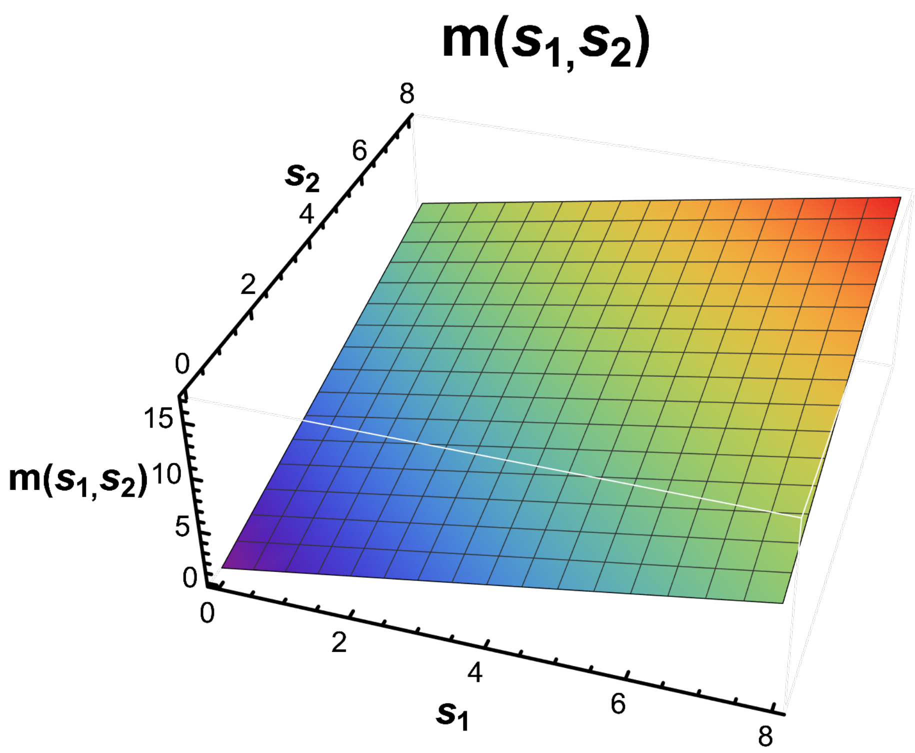
Out[16]= 2

So, $m_{12} > \{m_1, m_2\}$,

hence network *A* cannot show slope antagonism. The surface plots looks like –

In[17]:=
```
Plot3D[mP, {s1, 0, 8}, {s2, 0, 8}, AxesLabel →
  {Style["s1", Bold, 20, FontColor → Black], Style["s2", Bold, 20, FontColor → Black],
   Style["m(s1,s2)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s1,s2)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005],
 BoxStyle → GrayLevel[2], TicksStyle → Directive[Black, 15], ImageSize → Large]
```

Out[17]=



Network B

Equation for the dynamics of M -

In[248]:=
```
dmdt = km0 + km2 * s2 - kdm * m - km1 * s1 * m;
```

We can solve for m as -

In[249]:=
```
Solve[dmdt == 0, m]
```

Out[249]= $\left\{\left\{m \to \frac{k_{m0} + k_{m2}\, s_2}{k_{dm} + k_{m1}\, s_1}\right\}\right\}$

Surface map and derivatives of M

In[20]:= $mP = \frac{1 + 1 * s_2}{1 + 1 * s_1};$

In[21]:= $mP1 = 1 / (1 + s_1);$

$mP2 = 1 + s_2;$

The derivatives are,

In[23]:= $m_1 = D[mP1, s_1]$

Out[23]= $-\frac{1}{(1 + s_1)^2}$

In[24]:= $m_2 = D[mP2, s_2]$

Out[24]= 1

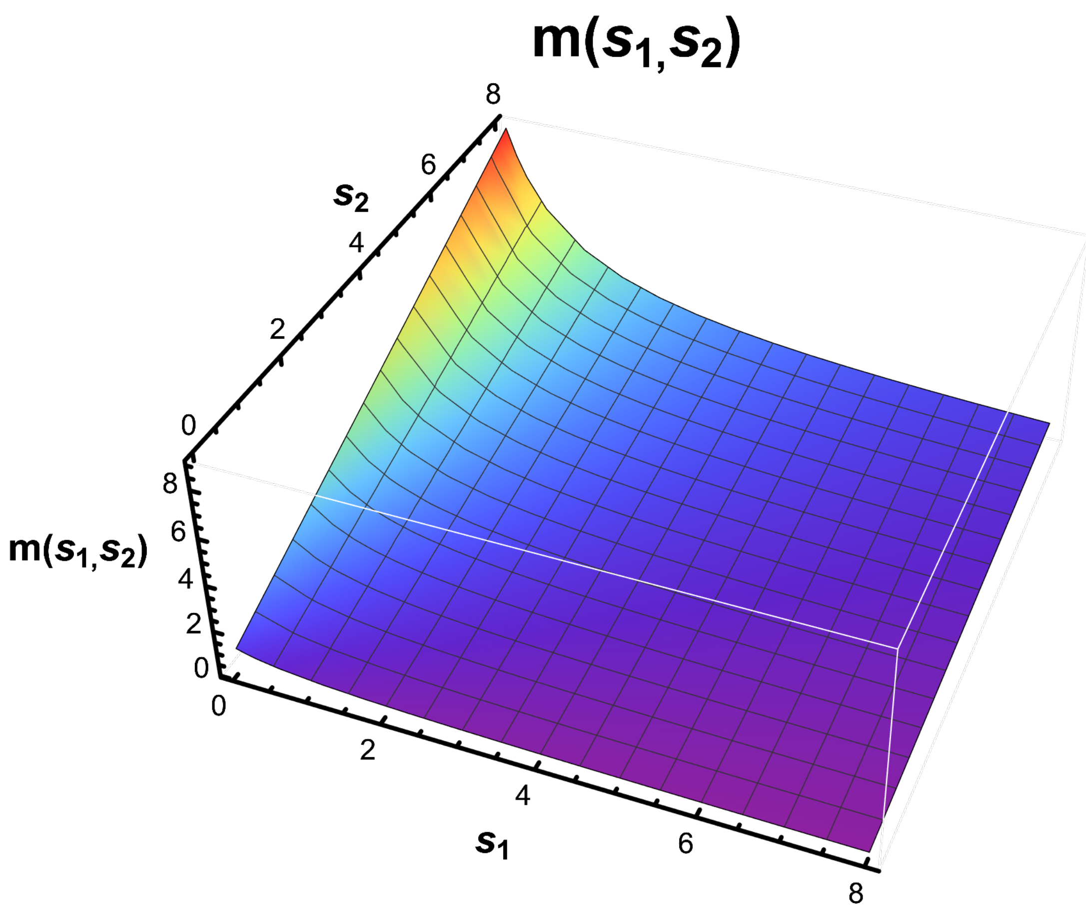
In[26]:= $m_{12} = FullSimplify[D[mP, s_1] + D[mP, s_2]]$

Out[26]= $\frac{s_1 - s_2}{(1 + s_1)^2}$

So, $m_1 < 0$, hence network *B* cannot satisfy the slope antagonism condition.

In[28]:=
```
Plot3D[mP, {s1, 0, 8}, {s2, 0, 8}, AxesLabel →
  {Style["s1", Bold, 20, FontColor → Black], Style["s2", Bold, 20, FontColor → Black],
   Style["m(s1,s2)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s1,s2)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
 TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

Out[28]=



Network C

Equation for the dynamics of M -

In[250]:=
```
dmdt = km0 - kdm * m - km1 * s1 * m - km2 * s2 * m;
```

The solution for m is-

In[251]:=
```
Solve[dmdt == 0, m]
```

Out[251]= $$\left\{\left\{m \to \frac{k_{m0}}{k_{dm} + k_{m1}\, s_1 + k_{m2}\, s_2}\right\}\right\}$$

Surface map and derivatives of M

In[31]:= $$mP = \frac{1}{1 + s_1 + s_2};$$

In[32]:= $mP1 = 1 / (1 + s_1);$

$mP2 = 1 / (1 + s_2);$

The derivatives are,

In[34]:= $m_1 = D[mP1, s_1]$

Out[34]= $$-\frac{1}{(1 + s_1)^2}$$

In[35]:= $m_2 = D[mP2, s_2]$

Out[35]= $$-\frac{1}{(1 + s_2)^2}$$

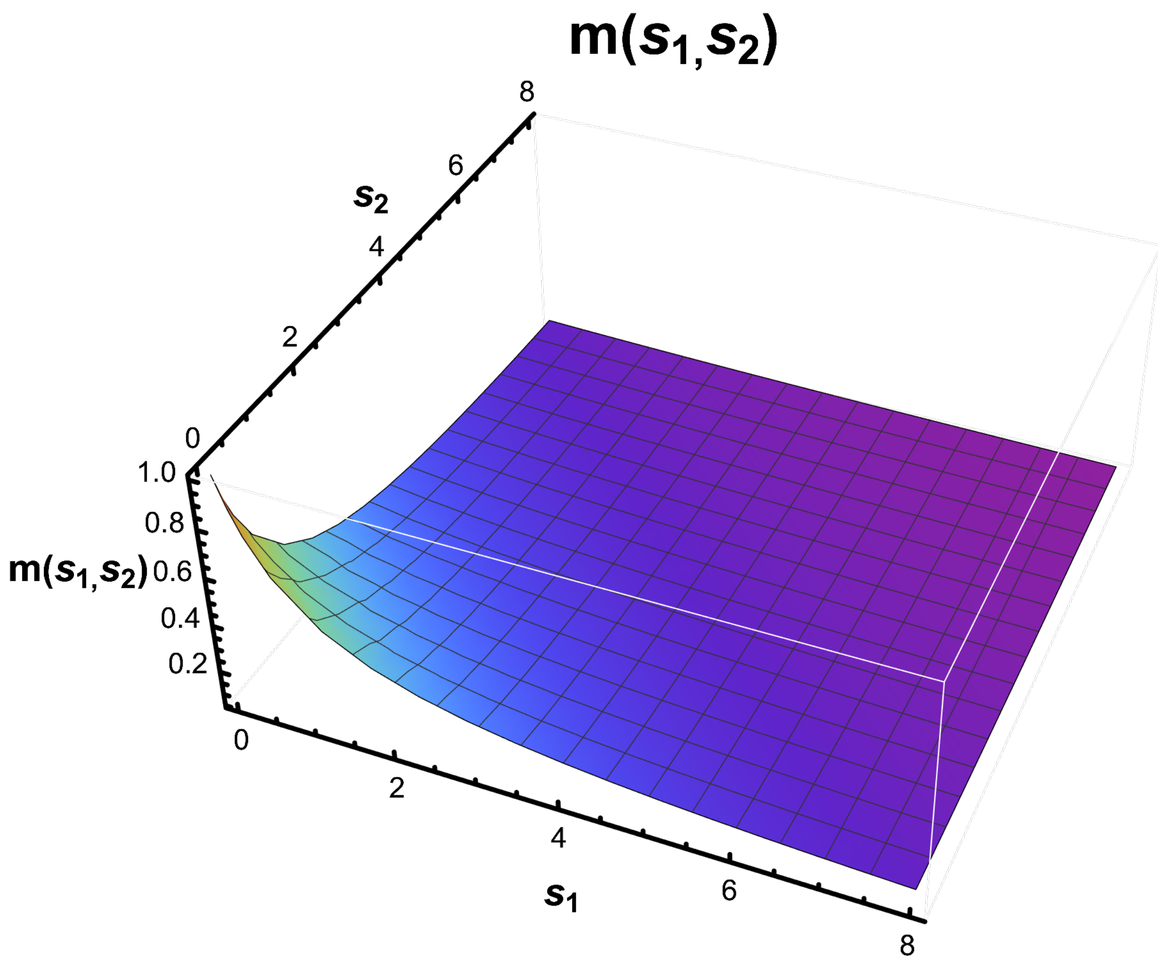
In[36]:= $m_{12} = \text{FullSimplify}[D[mP, s_1] + D[mP, s_2]]$

Out[36]= $$-\frac{2}{(1 + s_1 + s_2)^2}$$

So, $m_1 < 0$, $m_2 < 0$ hence network C cannot satisfy the slope antagonism condition.

In[37]:=
```
Plot3D[mP, {s1, 0, 8}, {s2, 0, 8}, AxesLabel →
  {Style["s1", Bold, 20, FontColor → Black], Style["s2", Bold, 20, FontColor → Black],
   Style["m(s1,s2)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s1,s2)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
 TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

Out[37]=



Network D

Equation for the dynamics of M -

In[252]:=
```
dmdt = km0 + km1 * s1 + km2 * s2 - (kdm + kmm * m) * m;
```

The solution for m is -

In[253]:= `Solve[dmdt == 0, m]`

Out[253]= $$\left\{\left\{m \to -\frac{k_{dm} - \sqrt{k_{dm}^2 + 4\,k_{mm}\,(k_{m0} + k_{m1}\,s_1 + k_{m2}\,s_2)}}{2\,k_{mm}}\right\}, \left\{m \to -\frac{k_{dm} + \sqrt{k_{dm}^2 + 4\,k_{mm}\,(k_{m0} + k_{m1}\,s_1 + k_{m2}\,s_2)}}{2\,k_{mm}}\right\}\right\}$$

Surface map and derivatives of M

In[40]:= $$mP = \frac{-1 + \sqrt{1 + 4 * (1 + s_1 + s_2)}}{2};$$

$$mP1 = \frac{-1 + \sqrt{1 + 4 * (1 + s_1)}}{2};$$

$$mP2 = \frac{-1 + \sqrt{1 + 4 * (1 + s_2)}}{2};$$

The derivatives are,

In[43]:= $m_1 = D[mP1, s_1]$

Out[43]= $$\frac{1}{\sqrt{1 + 4 \times (1 + s_1)}}$$

In[44]:= $m_2 = D[mP2, s_2]$

Out[44]= $$\frac{1}{\sqrt{1 + 4 \times (1 + s_2)}}$$

In[45]:= $m_{12} = \text{FullSimplify}[D[mP, s_1] + D[mP, s_2]]$

Out[45]= $$\frac{2}{\sqrt{5 + 4\,s_1 + 4\,s_2}}$$

In[70]:= $\text{FullSimplify}[m_{12}\text{^}2 - m_1\text{^}2]$

Out[70]= $$\frac{1}{-5 - 4\,s_1} + \frac{4}{5 + 4\,s_1 + 4\,s_2}$$

In[75]:= $\text{FullSimplify}[m_{12}\text{^}2 - m_2\text{^}2]$

Out[75]= $$\frac{1}{-5 - 4\,s_2} + \frac{4}{5 + 4\,s_1 + 4\,s_2}$$

In[74]:= $\text{Solve}[m_{12}\text{^}2 == m_1\text{^}2, s_2]$

Out[74]= $$\left\{\left\{s_2 \to \frac{3}{4} \times (5 + 4\,s_1)\right\}\right\}$$

So, if we want $m_{12} < m_1$ then we need $s_2 > \frac{3}{4} \times (5 + 4\,s_1)$

In[80]:=
```
Solve[m12^2 == m2^2, s2]
```

Out[80]= $\left\{\left\{s_2 \to \frac{1}{12} \times (-15 + 4\, s_1)\right\}\right\}$

So, if we want $m_{12} < m_2$ then we need $s_2 < \frac{1}{12} \times (-15 + 4\, s_1)$

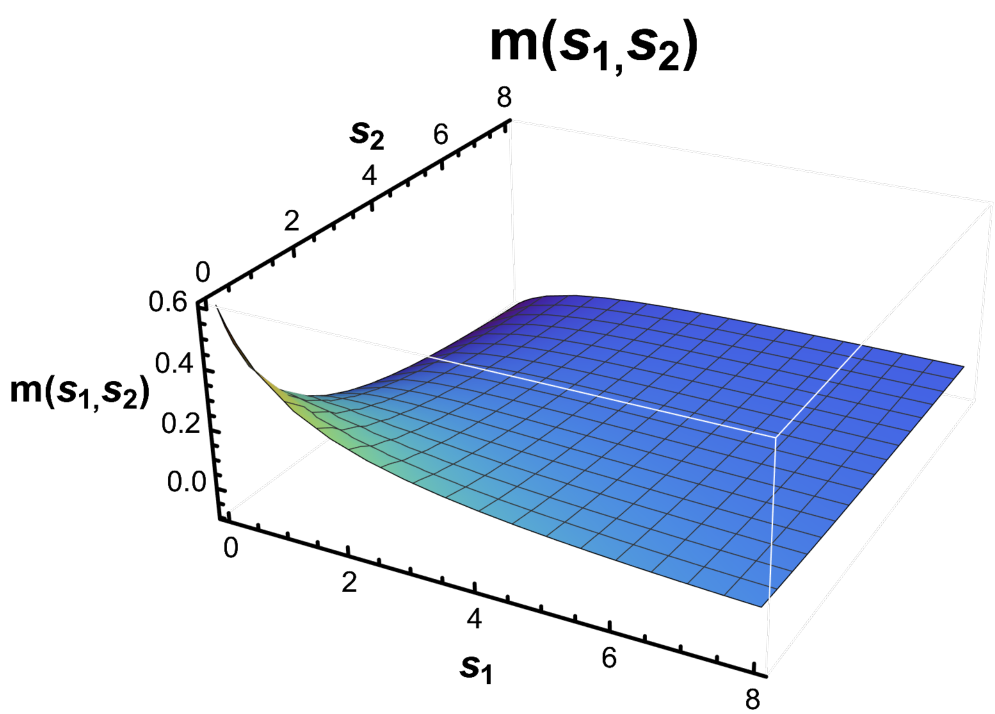
Now, to satisfy $m_{12} < \{m_1, m_2\}$ we need $\frac{3}{4} \times (5 + 4\, s_1) < s_2 < \frac{1}{12} \times (-15 + 4\, s_1)$.
Which can only be satisfied if
$\frac{3}{4} \times (5 + 4\, s_1) < \frac{1}{12} \times (-15 + 4\, s_1) \to s_1 < -15/8$. But we know s_1 must be positive.
So, the slope antagonism condition cannot be satisfied.

$s_{c21} = \frac{3}{4} \times (5 + 4\, s_1)$;

$s_{c22} = \frac{1}{12} \times (-15 + 4\, s_1)$;

In[73]:=
```
Plot3D[1/(-5 - 4 s1) + 4/(5 + 4 s1 + 4 s2), {s1, 0, 8}, {s2, 0, 8}, AxesLabel →
  {Style["s1", Bold, 20, FontColor → Black], Style["s2", Bold, 20, FontColor → Black],
   Style["m(s1,s2)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s1,s2)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
 TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

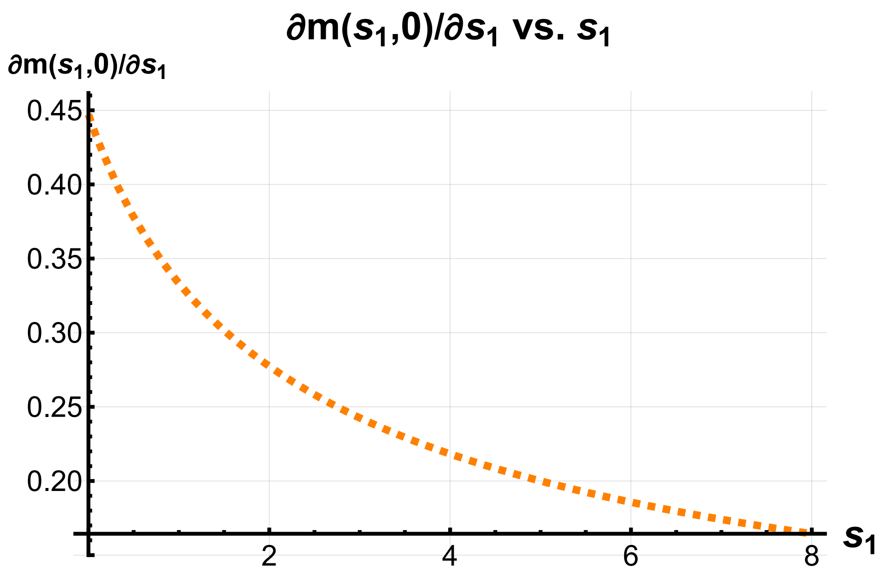
Out[73]=



Out[69]= $\frac{1}{-5-4\,s_1}+\frac{4}{5+4\,s_1+4\,s_2}$

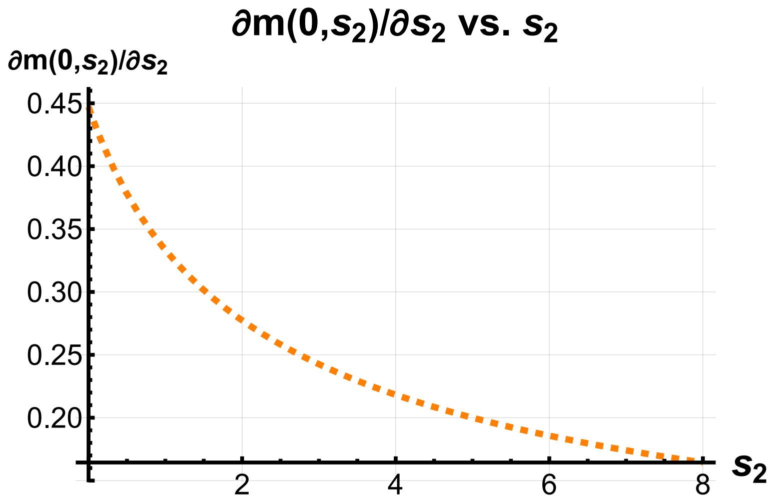
So, $m_1 = 1/(5+4s_1)$^0.5 =2 / (20 + 16 s_1) ^0.5 , m_2 =2 / (20 + 16 s_2) ^0.5

In[58]:=
```
plotset = {PlotStyle → Thick, AxesStyle → Thick,
    FrameStyle → Thick, TicksStyle → Directive[Black, 15]};
plotline1 = Plot[m₁, {s₁, 0, 8},
   AxesLabel → {Style["s₁", Bold, 20, FontColor → Black],
     Style["∂m(s₁,0)/∂s₁", Bold, 15, FontColor → Black]},
   PlotLabel → Style["∂m(s₁,0)/∂s₁ vs. s₁", Bold, 20, FontColor → Black],
   GridLines → Automatic,
   PlotStyle → {Orange, Dashed, Thickness[0.01]}, Evaluate@plotset]
```

Out[59]=


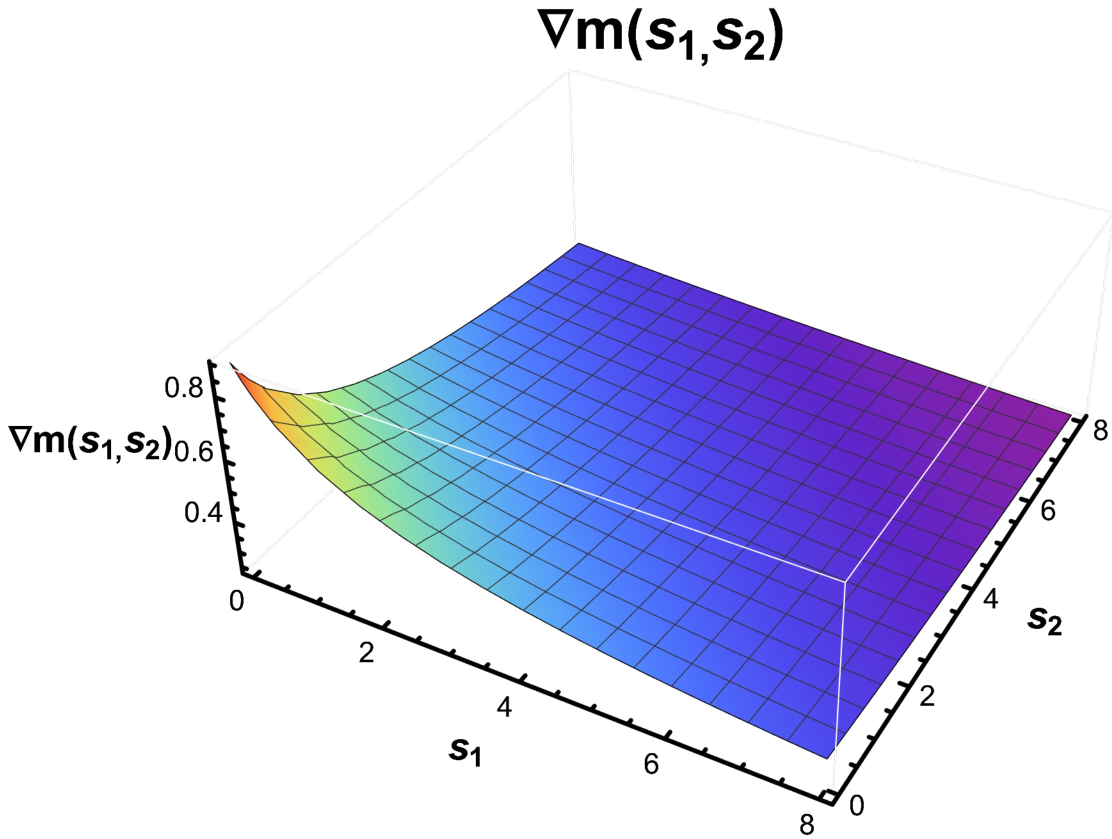
In[60]:=
```
plotline2 = Plot[m₂, {s₂, 0, 8},
  AxesLabel → {Style["s₂", Bold, 20, FontColor → Black],
    Style["∂m(0,s₂)/∂s₂", Bold, 15, FontColor → Black]},
  PlotLabel → Style["∂m(0,s₂)/∂s₂ vs. s₂", Bold, 20, FontColor → Black],
  GridLines → Automatic,
  PlotStyle → {Orange, Dashed, Thickness[0.01]}, Evaluate@plotset]
```

Out[60]=



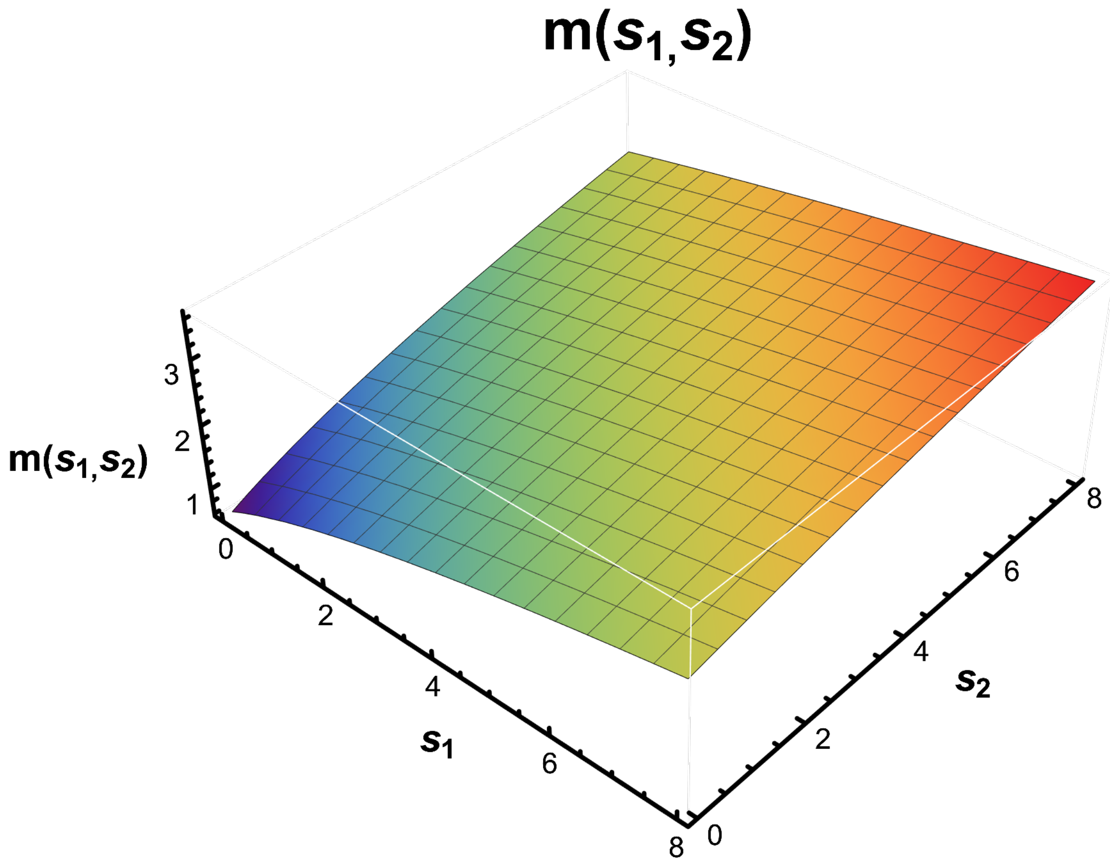
In[61]:=
```
plotsurface = Plot3D[m12, {s1, 0, 8}, {s2, 0, 8},
  AxesLabel → {Style["s1", Bold, 20, FontColor → Black], Style["s2", Bold, 20,
     FontColor → Black], Style["∇m(s1,s2)", Bold, 20, FontColor → Black]},
  PlotLabel → Style["∇m(s1,s2)", Bold, 30, FontColor → Black],
  ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
  TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

Out[61]=



In[65]:=
```
Plot3D[mP, {s1, 0, 8}, {s2, 0, 8}, AxesLabel →
  {Style["s1", Bold, 20, FontColor → Black], Style["s2", Bold, 20, FontColor → Black],
   Style["m(s1,s2)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s1,s2)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
 TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

Out[65]=



Network E

Dynamical equation for M-

In[254]:=
```
dmdt = km0 + km2 * s2 - (kdm + km1 * s1 + kmm * m) * m;
Solve[dmdt == 0, m]
```

Out[255]=

$$\left\{\left\{m \to -\frac{k_{dm} + k_{m1}\, s_1 - \sqrt{(-k_{dm} - k_{m1}\, s_1)^2 + 4\, k_{mm}\, (k_{m0} + k_{m2}\, s_2)}}{2\, k_{mm}}\right\},\right.$$
$$\left.\left\{m \to -\frac{k_{dm} + k_{m1}\, s_1 + \sqrt{(-k_{dm} - k_{m1}\, s_1)^2 + 4\, k_{mm}\, (k_{m0} + k_{m2}\, s_2)}}{2\, k_{mm}}\right\}\right\}$$

Using m>0 and setting all reaction rates to 1 for analysis we have-

In[257]:= $mP = \frac{-1 - s_1 + \sqrt{(-1 - s_1)^2 + 4 * (1 + s_2)}}{2};$

$mP1 = \frac{-1 - s_1 + \sqrt{(-1 - s_1)^2 + 4}}{2};$

$mP2 = \frac{-1 + \sqrt{1 + 4 * (1 + s_2)}}{2};$

Now we derive the derivatives

In[265]:= m_1 = FullSimplify[D[mP1, s_1]]

Out[265]= $\frac{1}{2} \times \left(-1 + \frac{1 + s_1}{\sqrt{5 + s_1 (2 + s_1)}}\right)$

In[268]:= FullSimplify[5 + s_1 (2 + s_1) - (1 + s_1) ^2]

Out[268]= 4

So, we can see that m_1<0. So, that is why network E fails.

In[263]:= m_2 = FullSimplify[D[mP2, s_2]]

Out[263]= $\frac{1}{\sqrt{5 + 4 s_2}}$

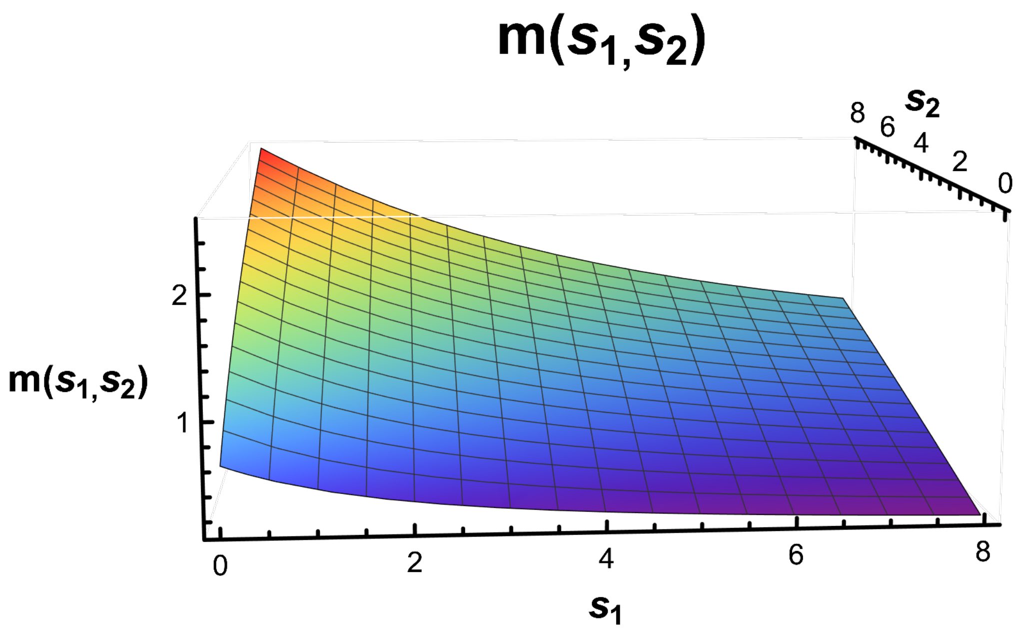
In[264]:= m_{12} = FullSimplify[D[mP, s_1] + D[mP, s_2]]

Out[264]= $\frac{3 + s_1 - \sqrt{5 + s_1 (2 + s_1) + 4 s_2}}{2 \sqrt{5 + s_1 (2 + s_1) + 4 s_2}}$

The surface plot-

In[269]:=
```
Plot3D[mP, {s1, 0, 8}, {s2, 0, 8}, AxesLabel →
  {Style["s1", Bold, 20, FontColor → Black], Style["s2", Bold, 20, FontColor → Black],
   Style["m(s1,s2)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s1,s2)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
 TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

Out[269]=



Network F

The dynamics of M is-

In[270]:=
```
dmdt = km0 - (kdm + km1 * s1 + km2 * s2 + kmm * m) * m;
Solve[dmdt == 0, m]
```

Out[271]=

$$\left\{\left\{m \to -\frac{k_{dm} + k_{m1}\, s_1 + k_{m2}\, s_2 - \sqrt{4\, k_{m0}\, k_{mm} + (-k_{dm} - k_{m1}\, s_1 - k_{m2}\, s_2)^2}}{2\, k_{mm}}\right\},\right.$$

$$\left.\left\{m \to -\frac{k_{dm} + k_{m1}\, s_1 + k_{m2}\, s_2 + \sqrt{4\, k_{m0}\, k_{mm} + (-k_{dm} - k_{m1}\, s_1 - k_{m2}\, s_2)^2}}{2\, k_{mm}}\right\}\right\}$$

To plot and analyse we set all reaction rates to 1 and use the condition that m>0-

In[272]:=
$$mP = \frac{-1 - s_1 - s_2 + \sqrt{4 + (-1 - s_1 - s_2)^2}}{2};$$
$$mP1 = \frac{-1 - s_1 + \sqrt{4 + (-1 - s_1)^2}}{2};$$
$$mP2 = \frac{-1 - s_2 + \sqrt{4 + (-1 - s_2)^2}}{2};$$

Derivative analysis for slope antagonism-

In[275]:= m_1 = FullSimplify[D[mP1, s_1]]

Out[275]= $$\frac{1}{2} \times \left(-1 + \frac{1 + s_1}{\sqrt{5 + s_1\ (2 + s_1)}}\right)$$

In[276]:= m_2 = FullSimplify[D[mP2, s_2]]

Out[276]= $$\frac{1}{2} \times \left(-1 + \frac{1 + s_2}{\sqrt{5 + s_2\ (2 + s_2)}}\right)$$

In[277]:= m_{12} = FullSimplify[D[mP, s_1] + D[mP, s_2]]

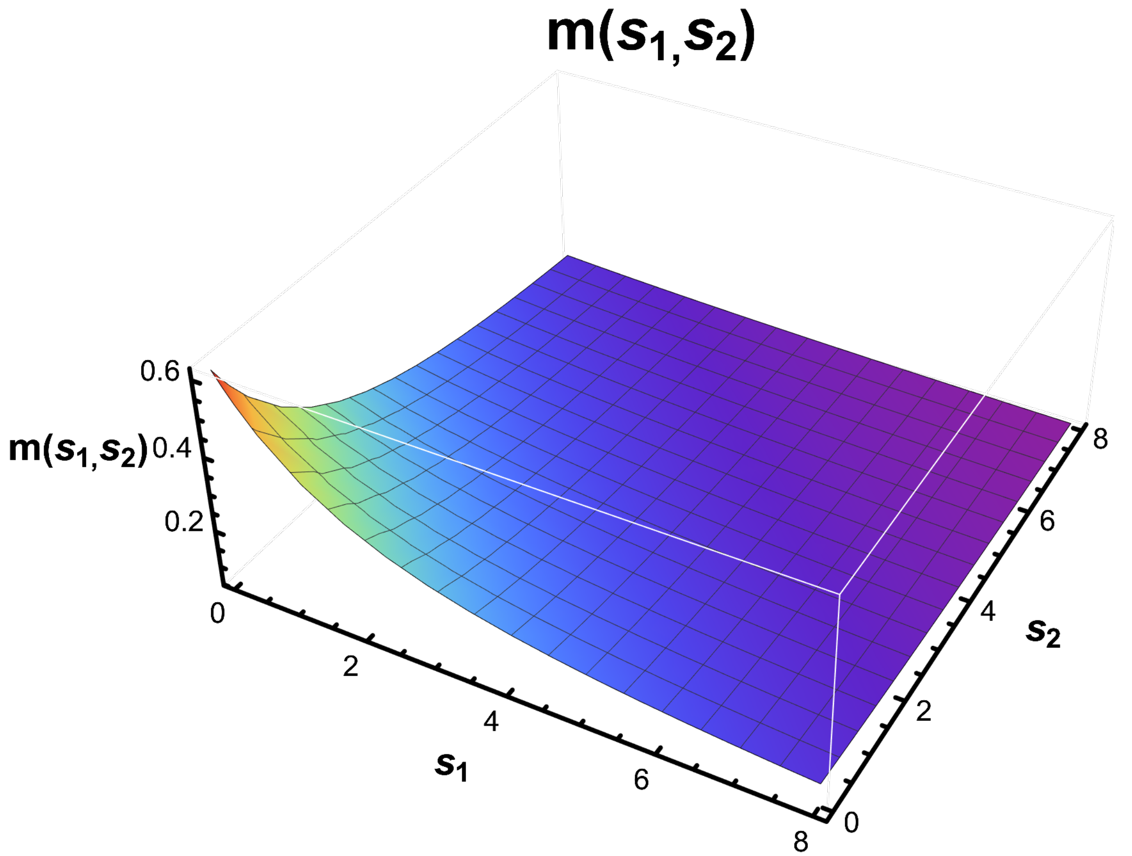
Out[277]= $$-1 + \frac{1 + s_1 + s_2}{\sqrt{4 + (1 + s_1 + s_2)^2}}$$

Using network E’s analysis we see $\{m_1, m_2\}$<0. So network F also fails.

Surface plot for m-

In[278]:=
```
Plot3D[mP, {s1, 0, 8}, {s2, 0, 8}, AxesLabel →
  {Style["s1", Bold, 20, FontColor → Black], Style["s2", Bold, 20, FontColor → Black],
   Style["m(s1,s2)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s1,s2)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
 TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

Out[278]=



Network G

The dynamics of M-

In[279]:=
```
dmdt = km0 + km1 * s1 + km2 * s2 - (kdm - kpm) * m;
Solve[dmdt == 0, m]
```

Out[280]= $\left\{\left\{m \to \frac{k_{m0} + k_{m1}\, s_1 + k_{m2}\, s_2}{k_{dm} - k_{pm}}\right\}\right\}$

Now for positivity of m and to have a steady state solution we need
$k_{dm} > k_{pm}$. So, in this case, for further analysis we set all rates except k_{dm} to 1 and set $k_{dm} = 2$.

In[281]:=
```
mP = 1 + s1 + s2;
mP1 = 1 + s1;
mP2 = 1 + s2;
```

The derivatives of m-

In[284]:=
```
m1 = FullSimplify[D[mP1, s1]]
```

Out[284]= 1

In[285]:=
```
m2 = FullSimplify[D[mP2, s2]]
```

Out[285]= 1

In[286]:=
```
m12 = FullSimplify[D[mP, s1] + D[mP, s2]]
```

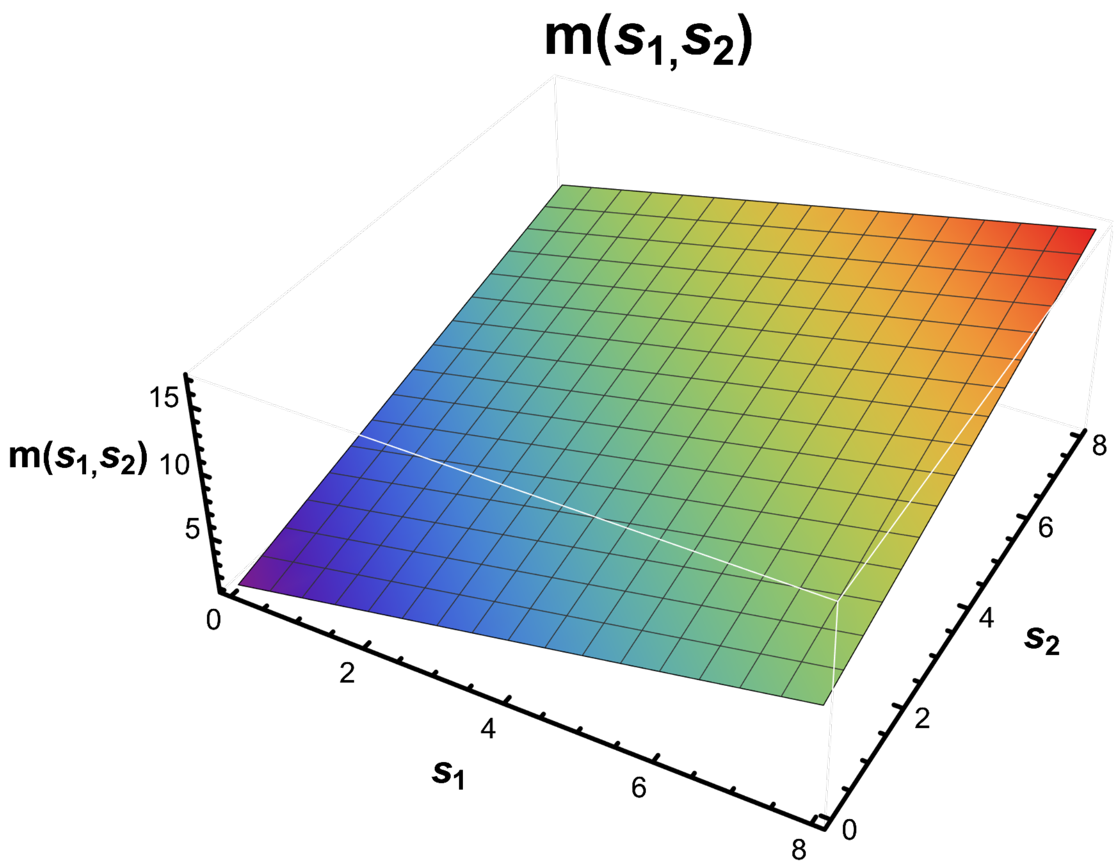
Out[286]= 2

So, in this case $m_{12} > \{m_1, m_2\}$, that is why network G fails.

Surface plot of m-

In[287]:=
```
Plot3D[mP, {s1, 0, 8}, {s2, 0, 8}, AxesLabel →
  {Style["s1", Bold, 20, FontColor → Black], Style["s2", Bold, 20, FontColor → Black],
   Style["m(s1,s2)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s1,s2)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
 TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

Out[287]=

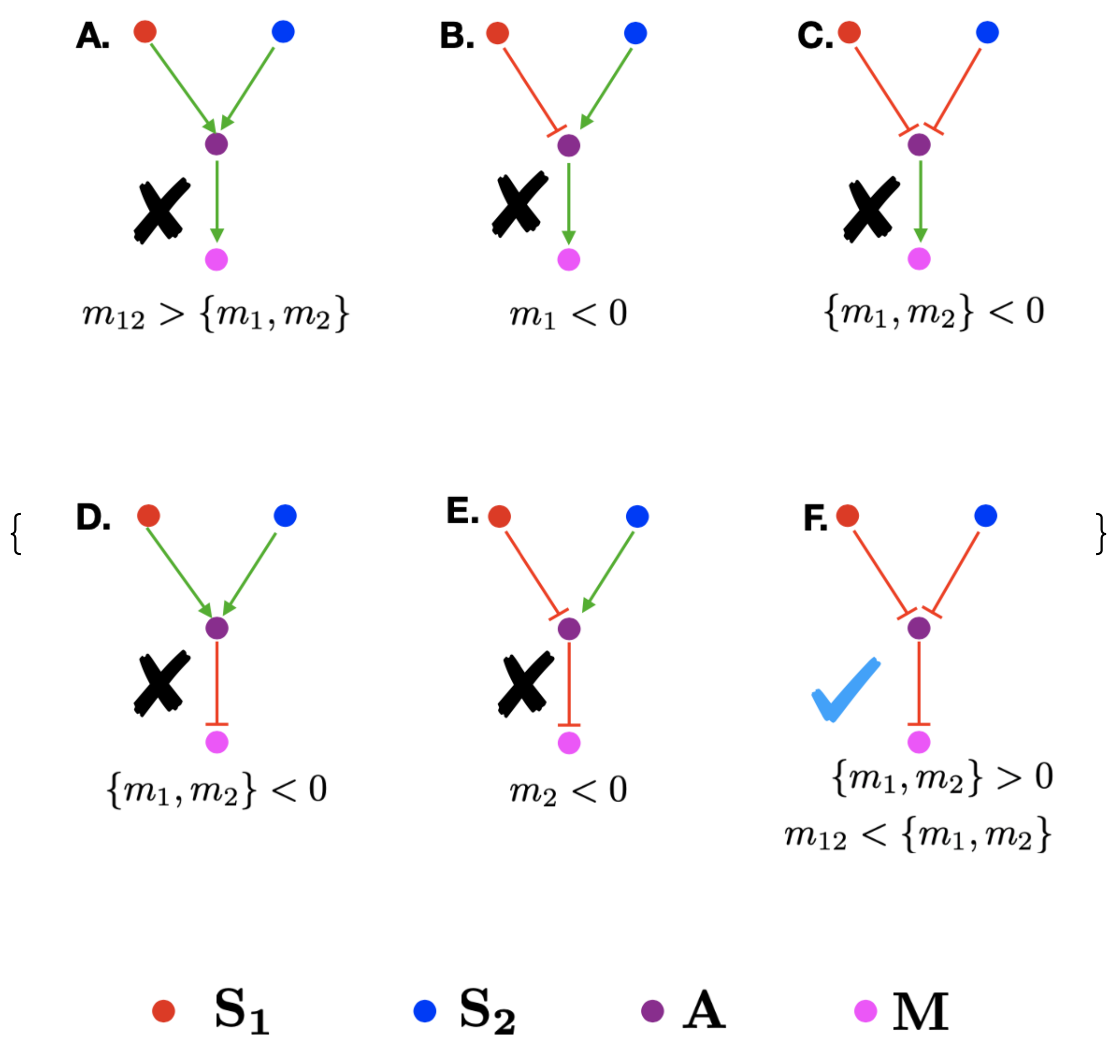


Now network H and I will have the exact same characteristics as network B and C respectively, and they will be unsuccessful for the same reasons.

We now analyse four node three edge networks.

Four node three edges regulatory networks

We consider these six unique four node three edges regulatory networks-



Now, in networks A,B,C m is produced by A using a simple production reaction. So, in these networks M will behave in exactly the same way as in the corresponding three node networks A,B,C respectively. Hence, networks A,B,C are unsuccessful to explain the slope antagonism for exactly the same reasons as in the three node case. Now, we analyze networks D-F.

Network D

Dynamics of A and M-

In[288]:=
```
dadt = k_a0 + k_a1 * s_1 + k_a2 * s_2 - k_da * a;
dmdt = k_m0 - (k_dm + k_am * a) * m;
Solve[{dadt == 0, dmdt == 0}, {a, m}]
```

Out[290]= $\left\{\left\{a \to \frac{k_{a0} + k_{a1}\, s_1 + k_{a2}\, s_2}{k_{da}},\; m \to \frac{k_{da}\, k_{m0}}{k_{a0}\, k_{am} + k_{da}\, k_{dm} + k_{a1}\, k_{am}\, s_1 + k_{a2}\, k_{am}\, s_2}\right\}\right\}$

We take the value of each parameter to be 1 then m is-

In[291]:=
```
mP = 1 / (2 + s_1 + s_2);
mP1 = 1 / (2 + s_1);
mP2 = 1 / (2 + s_2);
```

We now calculate the derivatives-

In[294]:=
```
m_1 = FullSimplify[D[mP1, s_1]]
```

Out[294]= $-\frac{1}{(2 + s_1)^2}$

In[295]:=
```
m_2 = FullSimplify[D[mP2, s_2]]
```

Out[295]= $-\frac{1}{(2 + s_2)^2}$

In[296]:=
```
m_12 = FullSimplify[D[mP, s_1] + D[mP, s_2]]
```

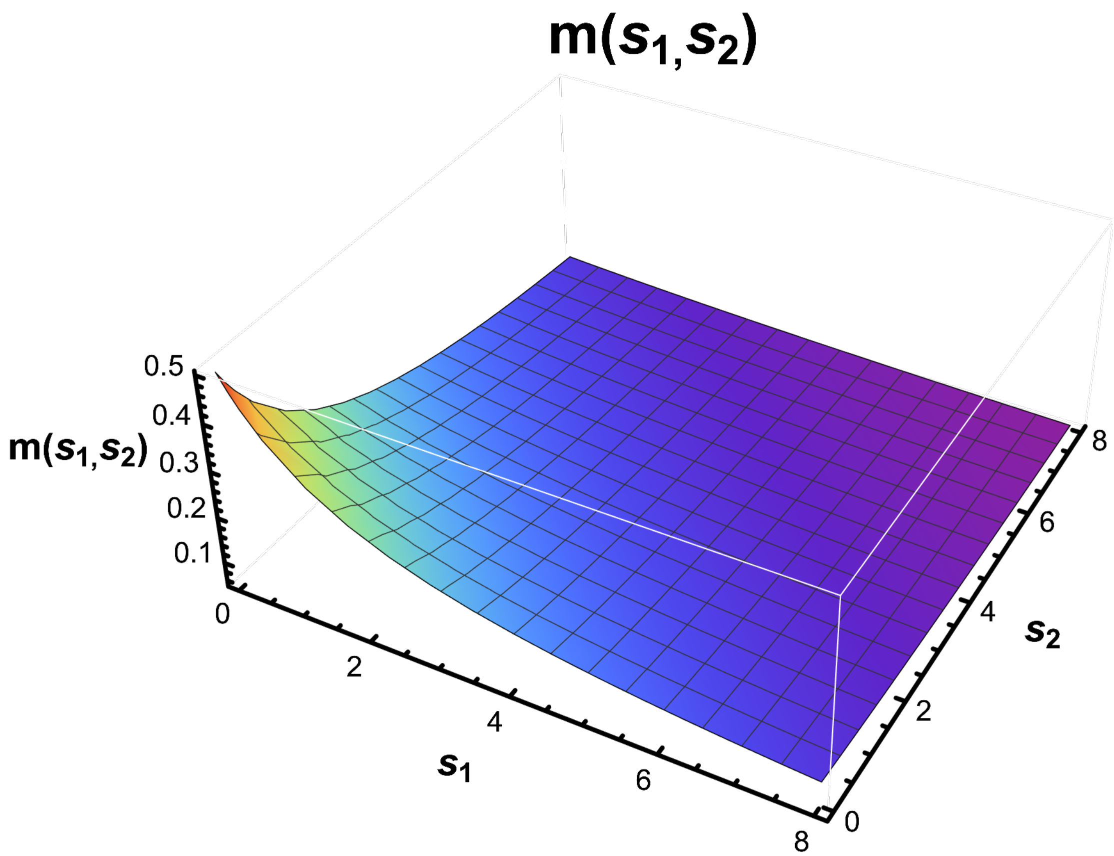
Out[296]= $-\frac{2}{(2 + s_1 + s_2)^2}$

Here, we have $\{m_1, m_2\}$<0. So, network D fails.

Surface plot of m-

In[297]:=
```
Plot3D[mP, {s1, 0, 8}, {s2, 0, 8}, AxesLabel →
  {Style["s1", Bold, 20, FontColor → Black], Style["s2", Bold, 20, FontColor → Black],
   Style["m(s1,s2)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s1,s2)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
 TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

Out[297]=



Network E

The dynamics of A,M-

In[298]:=
```
dadt = ka0 + ka2 * s2 - (kda + ka1 * s1) * a;
dmdt = km0 - (kdm + kam * a) * m;
Solve[{dadt == 0, dmdt == 0}, {a, m}]
```

Out[300]= $\left\{\left\{a \to \frac{k_{a0} + k_{a2}\, s_2}{k_{da} + k_{a1}\, s_1},\ m \to \frac{k_{m0}\, (k_{da} + k_{a1}\, s_1)}{k_{a0}\, k_{am} + k_{da}\, k_{dm} + k_{a1}\, k_{dm}\, s_1 + k_{a2}\, k_{am}\, s_2}\right\}\right\}$

For plotting we take each parameter value to be 1. Then we have,

In[301]:=
```
mP = (1 + s1) / (2 + s1 + s2);
mP1 = (1 + s1) / (2 + s1);
mP2 = 1 / (2 + s2);
```

Calculating the derivatives,

In[304]:=
```
m1 = FullSimplify[D[mP1, s1]]
```

Out[304]= $\frac{1}{(2+s_1)^2}$

In[305]:=
```
m2 = FullSimplify[D[mP2, s2]]
```

Out[305]= $-\frac{1}{(2+s_2)^2}$

In[306]:=
```
m12 = FullSimplify[D[mP, s1] + D[mP, s2]]
```

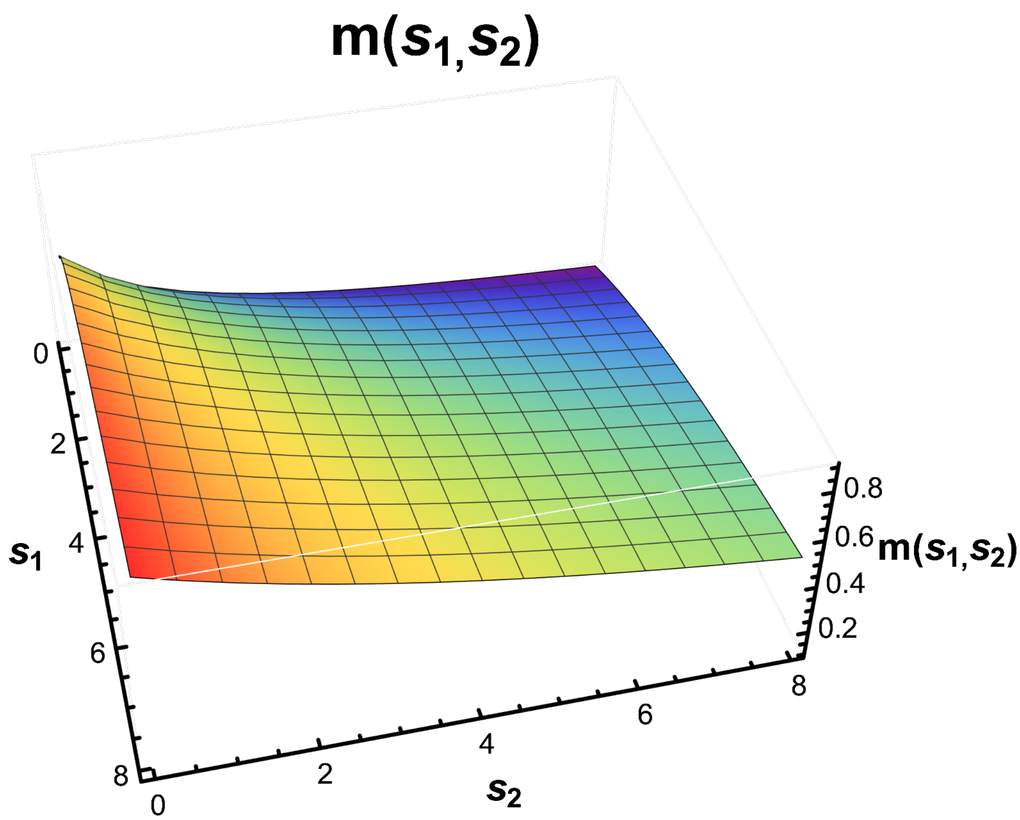
Out[306]= $\frac{-s_1+s_2}{(2+s_1+s_2)^2}$

Here, we have $m_2 < 0$. So, network E fails.

Surface plot of m-

In[307]:=
```
Plot3D[mP, {s₁, 0, 8}, {s₂, 0, 8}, AxesLabel →
  {Style["s₁", Bold, 20, FontColor → Black], Style["s₂", Bold, 20, FontColor → Black],
   Style["m(s₁,s₂)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s₁,s₂)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
 TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

Out[307]=



Network F

The dynamics of A,M is-

In[308]:=
```
dadt = k_a0 - (k_da + k_a1 * s_1 + k_a2 * s_2) * a;
dmdt = k_m0 - (k_dm + k_am * a) * m;
Solve[{dadt == 0, dmdt == 0}, {a, m}]
```

Out[310]= $\left\{\left\{a \to \frac{k_{a0}}{k_{da} + k_{a1}\, s_1 + k_{a2}\, s_2},\ m \to \frac{k_{m0}\,(k_{da} + k_{a1}\, s_1 + k_{a2}\, s_2)}{k_{a0}\, k_{am} + k_{da}\, k_{dm} + k_{a1}\, k_{dm}\, s_1 + k_{a2}\, k_{dm}\, s_2}\right\}\right\}$

For plotting we set all parameter values to 1,

In[311]:=
```
mP = (1 + s_1 + s_2) / (2 + s_1 + s_2);
mP1 = (1 + s_1) / (2 + s_1);
mP2 = (1 + s_2) / (2 + s_2);
```

The derivatives are,

In[314]:=
```
m_1 = FullSimplify[D[mP1, s_1]]
```

Out[314]= $\frac{1}{(2 + s_1)^2}$

In[315]:=
```
m_2 = FullSimplify[D[mP2, s_2]]
```

Out[315]= $\frac{1}{(2 + s_2)^2}$

In[316]:=
```
m_12 = FullSimplify[D[mP, s_1] + D[mP, s_2]]
```

Out[316]= $\frac{2}{(2 + s_1 + s_2)^2}$

In[322]:=
```
FullSimplify[m_12 - m_2]
```

Out[322]= $-\frac{1}{(2 + s_2)^2} + \frac{2}{(2 + s_1 + s_2)^2}$

In[331]:=
```
Solve[m_12 == m_1, s_2]
```

Out[331]= $\left\{\left\{s_2 \to -2 - s_1 - \sqrt{2}\ \sqrt{4 + 4\, s_1 + s_1^2}\right\},\ \left\{s_2 \to -2 - s_1 + \sqrt{2}\ \sqrt{4 + 4\, s_1 + s_1^2}\right\}\right\}$

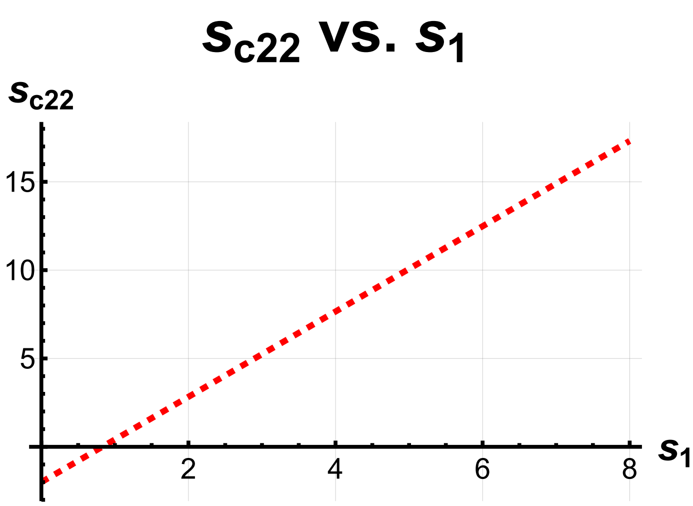
In[328]:=
```
s_c21 = (2 + s_1) * (√2 - 1);
s_c22 = s_1 * (√2 + 1) - 2;
FullSimplify[s_c22 - s_c21]
```

Out[330]= $-2\,\sqrt{2} + 2\, s_1$

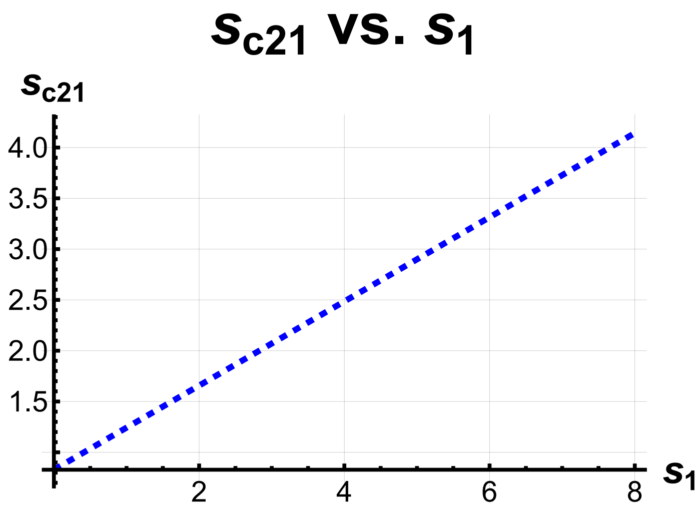
We want $s_{c21} < s_2 < s_{c22}$.

In[336]:=
```
plotset = {PlotStyle → Thick, AxesStyle → Thick,
   FrameStyle → Thick, TicksStyle → Directive[Black, 15]};
plot1 = Plot[sc22, {s1, 0, 8},
  AxesLabel → {Style["s1", Bold, 20, FontColor → Black],
    Style["sc22", Bold, 20, FontColor → Black]},
  PlotLabel → Style["sc22 vs. s1", Bold, 30, FontColor → Black],
  GridLines → Automatic,
  PlotStyle → {Red, Dashed, Thickness[0.01]}, Evaluate@plotset]
plot2 = Plot[sc21, {s1, 0, 8},
  AxesLabel → {Style["s1", Bold, 20, FontColor → Black],
    Style["sc21", Bold, 20, FontColor → Black]},
  PlotLabel → Style["sc21 vs. s1", Bold, 30, FontColor → Black],
  GridLines → Automatic,
  PlotStyle → {Blue, Dashed, Thickness[0.01]}, Evaluate@plotset]
Legended[Show[plot1, plot2, PlotLabel → "Critical s2 values",
  AxesLabel → {"s1", "sc2(s1)"},
  PlotRange → All,
  GridLines → Automatic],
 SwatchLegend[{Red, Blue}, {"sc22", "sc21"}]]
```

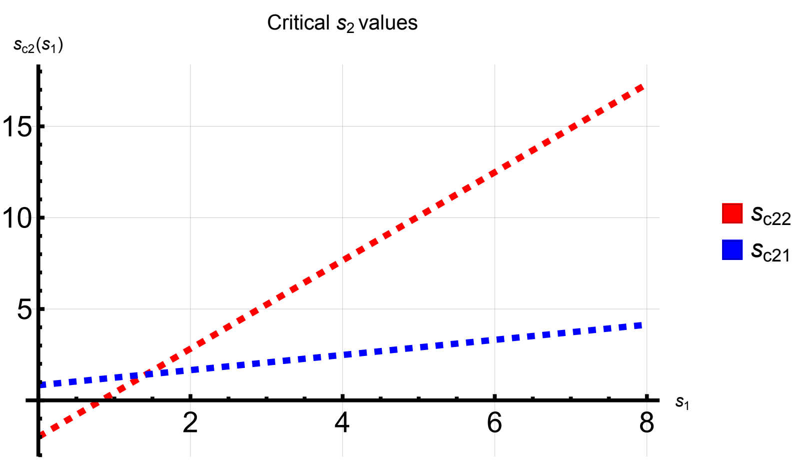
Out[337]=



Out[338]=



Out[339]=



So we can have $\{m_1, m_2\}$>0 and m_{12} <$\{m_1, m_2\}$, for a set of values of (s_1, s_2). Hence slope antagonism can be satisfied by Network F.

Surface plot of m-

In[340]:=
```
Plot3D[mP, {s₁, 0, 8}, {s₂, 0, 8}, AxesLabel →
  {Style["s₁", Bold, 20, FontColor → Black], Style["s₂", Bold, 20, FontColor → Black],
   Style["m(s₁,s₂)", Bold, 20, FontColor → Black]},
 PlotLabel → Style["m(s₁,s₂)", Bold, 30, FontColor → Black],
 ColorFunction → "Rainbow", AxesStyle → Thickness[0.005], BoxStyle → GrayLevel[2],
 TicksStyle → Directive[Black, 15], ImageSize → Large, PlotRange → Full]
```

Out[340]=