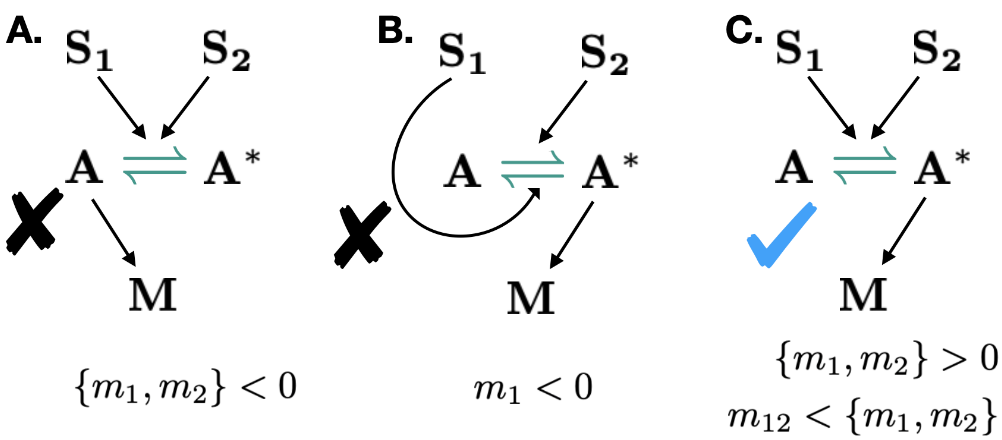
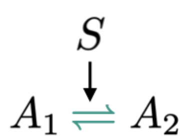
Minimal conversion network for slope antagonism

In this section we analyse three possible networks given in the picture below to find out the unique network that can satisfy slope antagonism-



For the derivations we use the math -



$$\dot{a_2} = k_1 s a_1 - k_2 a_2$$
$$a_1 + a_2 = k_0$$

Network A

The dynamics of A and M is given by,

In[409]:=
```
dadt = kB * (a0 - a) - (kF + k1 * s1 + k2 * s2) * a;
dmdt = km0 + kma * a - kdm * m;
Solve[{dadt == 0, dmdt == 0}, {a, m}]
```

Out[411]= $\left\{\left\{a \to \frac{a0\, k_B}{k_B + k_F + k_1 s_1 + k_2 s_2},\ m \to -\frac{-k_B k_{m0} - k_F k_{m0} - a0\, k_B k_{ma} - k_1 k_{m0} s_1 - k_2 k_{m0} s_2}{k_{dm} \left(k_B + k_F + k_1 s_1 + k_2 s_2\right)}\right\}\right\}$

For the analysis we set all reaction rates to 1 and a0=1. then,

In[412]:=
$$mP = \frac{3 + s_1 + s_2}{2 + s_1 + s_2};$$
$$mP1 = \frac{3 + s_1}{2 + s_1};$$
$$mP2 = \frac{3 + s_2}{2 + s_2};$$

The derivatives are,

In[415]:= m_1 = FullSimplify[D[mP1, s_1]]

Out[415]=
$$-\frac{1}{(2 + s_1)^2}$$

In[416]:= m_2 = FullSimplify[D[mP2, s_2]]

Out[416]=
$$-\frac{1}{(2 + s_2)^2}$$

In[417]:= m_{12} = FullSimplify[D[mP, s_1] + D[mP, s_2]]

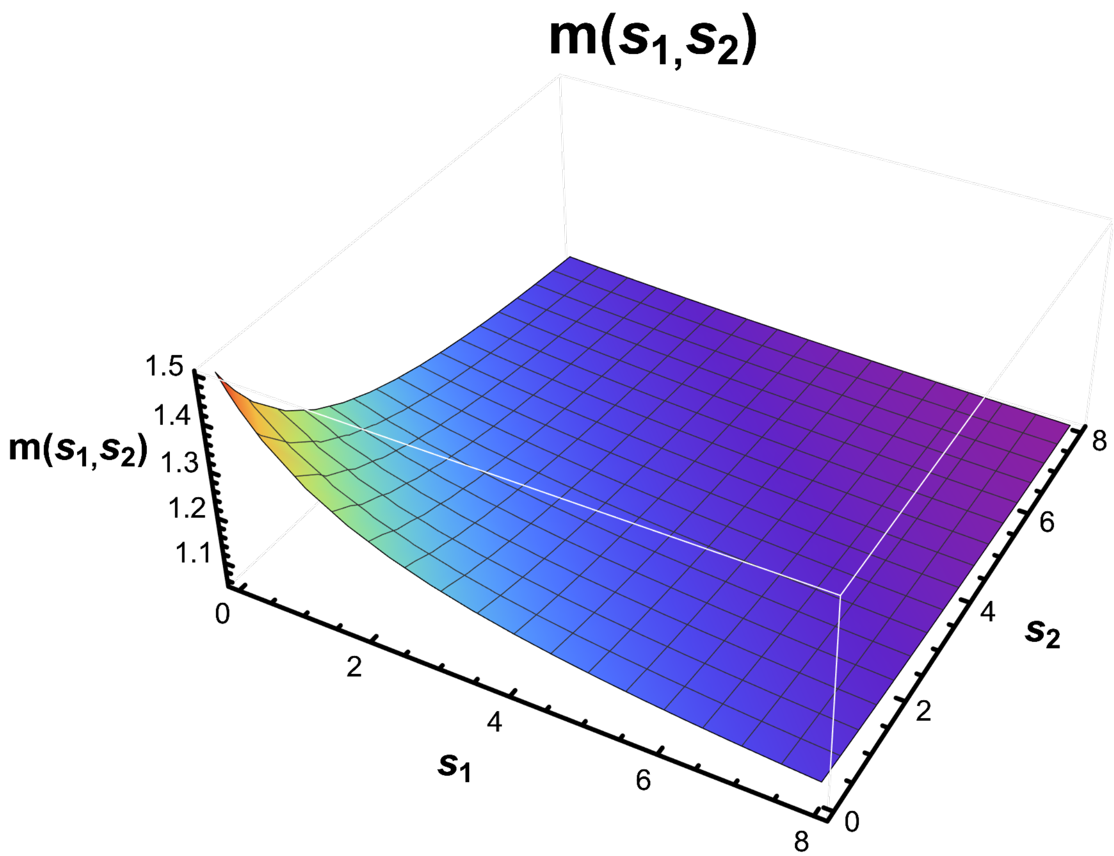
Out[417]=
$$-\frac{2}{(2 + s_1 + s_2)^2}$$

Since $\{m_1, m_2\}<0$, so network A cannot satisfy the slope antagonism condition.

Surface plot of m-

In[418]:=
```
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[418]=



Network B

Dynamics of A,M-

In[419]:=
```
dadt = (kB + k1 * s1) * (a0 - a) - (kF + k2 * s2) * a;
dmdt = km0 + kma * (a0 - a) - kdm * m;
Solve[{dadt == 0, dmdt == 0}, {a, m}]
```

Out[421]=

$$\left\{\left\{a \to \frac{a0\ (k_B + k_1\ s_1)}{k_B + k_F + k_1\ s_1 + k_2\ s_2},\ m \to -\frac{-k_B\ k_{m0} - k_F\ k_{m0} - a0\ k_F\ k_{ma} - k_1\ k_{m0}\ s_1 - k_2\ k_{m0}\ s_2 - a0\ k_2\ k_{ma}\ s_2}{k_{dm}\ (k_B + k_F + k_1\ s_1 + k_2\ s_2)}\right\}\right\}$$

For the analysis we set all reaction rates to 1 and a0 = 1. then,

In[426]:=
$$mP = \frac{3 + s_1 + 2 * s_2}{2 + s_1 + s_2};$$
$$mP1 = \frac{3 + s_1}{2 + s_1};$$
$$mP2 = \frac{3 + 2 * s_2}{2 + s_2};$$

Derivatives,

In[429]:=
```
m_1 = FullSimplify[D[mP1, s_1]]
```

Out[429]=
$$-\frac{1}{(2 + s_1)^2}$$

In[430]:=
```
m_2 = FullSimplify[D[mP2, s_2]]
```

Out[430]=
$$\frac{1}{(2 + s_2)^2}$$

In[431]:=
```
m_12 = FullSimplify[D[mP, s_1] + D[mP, s_2]]
```

Out[431]=
$$\frac{s_1 - s_2}{(2 + s_1 + s_2)^2}$$

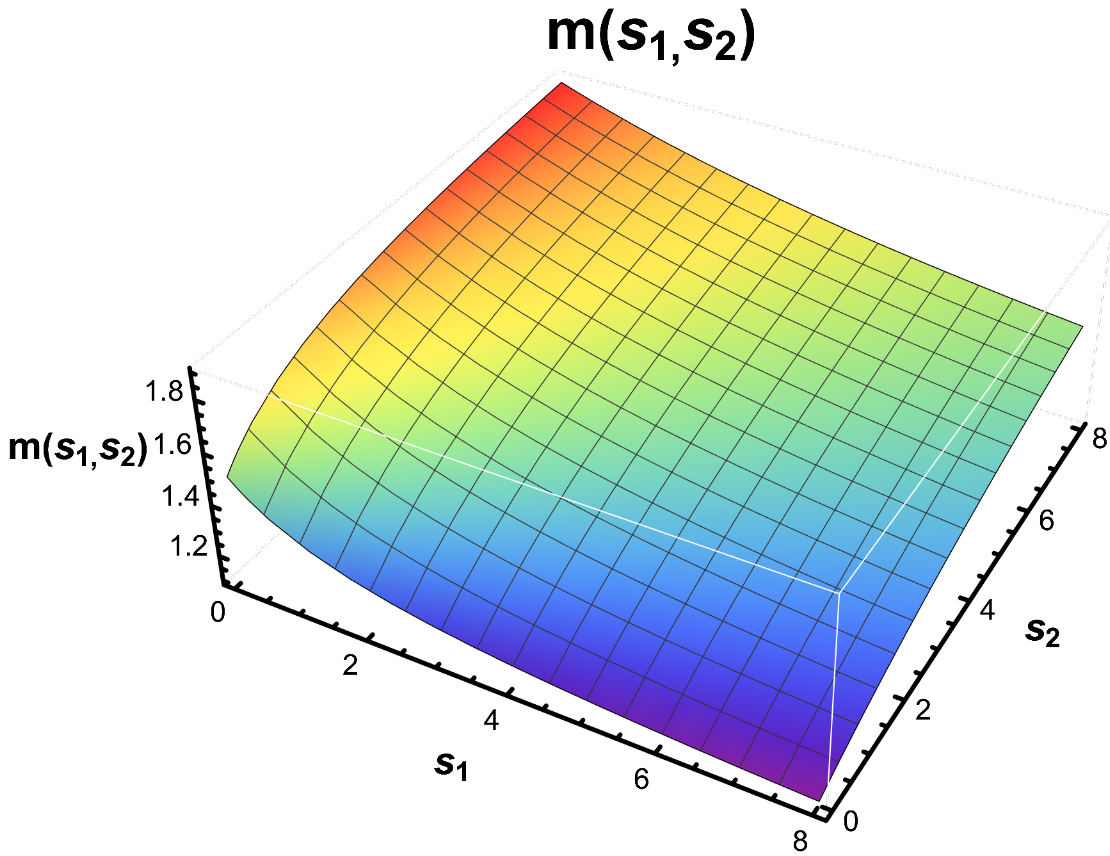
Since $m_1 < 0$,

so network B cannot satisfy the slope antagonism condition.

Surface plot,

In[432]:=
```
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[432]=



Network C

Dynamics

In[433]:=
```
dadt = kB * (a0 - a) - (kF + k₁ * s₁ + k₂ * s₂) * a;
dmdt = km0 + kma * (a0 - a) - kdm * m;
Solve[{dadt == 0, dmdt == 0}, {a, m}]
```

Out[435]=

$$\left\{\left\{a \to \frac{a0\, k_B}{k_B + k_F + k_1\, s_1 + k_2\, s_2},\right.\right.$$
$$\left.\left.m \to -\frac{-k_B\, k_{m0} - k_F\, k_{m0} - a0\, k_F\, k_{ma} - k_1\, k_{m0}\, s_1 - a0\, k_1\, k_{ma}\, s_1 - k_2\, k_{m0}\, s_2 - a0\, k_2\, k_{ma}\, s_2}{k_{dm}\, (k_B + k_F + k_1\, s_1 + k_2\, s_2)}\right\}\right\}$$

In[436]:=
$$mP = \frac{3 + 2 * s_1 + 2 * s_2}{2 + s_1 + s_2};$$
$$mP1 = \frac{3 + 2 * s_1}{2 + s_1};$$
$$mP2 = \frac{3 + 2 * s_2}{2 + s_2};$$

In[439]:= m_1 = FullSimplify[D[mP1, s_1]]

Out[439]=
$$\frac{1}{(2 + s_1)^2}$$

In[440]:= m_2 = FullSimplify[D[mP2, s_2]]

Out[440]=
$$\frac{1}{(2 + s_2)^2}$$

In[441]:= m_{12} = FullSimplify[D[mP, s_1] + D[mP, s_2]]

Out[441]=
$$\frac{2}{(2 + s_1 + s_2)^2}$$

The expression for the derivatives m_1, m_2 and m_{12} are the same as that in the four node three edges network F in the regulation case (Appendix A, Fig. 8F). We have shown that this can satisfy slope antagonism. Hence, network C can satisfy slope antagonism.

In[442]:=
```
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[442]=