Cooperation increases robustness to ecological disturbance in microbial cross-feeding networks

Generating Random Networks

Functions to calculate Entropy and Assortativity

Entropy

Assortativity

1. Colimitation model

Solving the system of ODE

The function “fNewSaitoKIC” solves the ODE system and gives the population at steady state of the system, starting with arbitrary initial conditions.

In[7420]:=

```
fNewSaitoKIC[Net_] := (

  dB1 =
   B1[t] (-B1[t] κ1 + nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) *
        M5[t]/(denK + M5[t])) - (c1,1 + c1,2 + c1,3 + c1,4 + c1,5) B1[t];
  dB2 = B2[t] (-B2[t] κ2 + nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) *
        M4[t]/(denK + M4[t]) * M5[t]/(denK + M5[t])) - (c2,1 + c2,2 + c2,3 + c2,4 + c2,5) B2[t];
  dB3 = B3[t] (-B3[t] κ3 + nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) *
```

```
        M4[t]/(denK + M4[t]) * M5[t]/(denK + M5[t])) - (c3,1 + c3,2 + c3,3 + c3,4 + c3,5) B3[t];
dB4 = B4[t] (-B4[t] κ4 + nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) *
        M4[t]/(denK + M4[t]) * M5[t]/(denK + M5[t])) - (c4,1 + c4,2 + c4,3 + c4,4 + c4,5) B4[t];
dB5 = B5[t] (-B5[t] κ5 + nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) *
        M4[t]/(denK + M4[t]) * M5[t]/(denK + M5[t])) - (c5,1 + c5,2 + c5,3 + c5,4 + c5,5) B5[t];

dM1 = -M1[t] q1 +
   (nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) * M5[t]/(denK + M5[t]))
    (-B1[t] d1,1 - B2[t] d1,2 - B3[t] d1,3 - B4[t] d1,4 - B5[t] d1,5) +
   B1[t] Ω1,1 + B2[t] Ω1,2 + B3[t] Ω1,3 + B4[t] Ω1,4 + B5[t] Ω1,5;
dM2 = -M2[t] q2 + (nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) *
       M5[t]/(denK + M5[t])) (-B1[t] d2,1 - B2[t] d2,2 - B3[t] d2,3 - B4[t] d2,4 - B5[t] d2,5) +
   B1[t] Ω2,1 + B2[t] Ω2,2 + B3[t] Ω2,3 + B4[t] Ω2,4 + B5[t] Ω2,5;
dM3 = -M3[t] q3 + (nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) *
       M5[t]/(denK + M5[t])) (-B1[t] d3,1 - B2[t] d3,2 - B3[t] d3,3 - B4[t] d3,4 - B5[t] d3,5) +
   B1[t] Ω3,1 + B2[t] Ω3,2 + B3[t] Ω3,3 + B4[t] Ω3,4 + B5[t] Ω3,5;
dM4 = -M4[t] q4 + (nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) *
       M5[t]/(denK + M5[t])) (-B1[t] d4,1 - B2[t] d4,2 - B3[t] d4,3 - B4[t] d4,4 - B5[t] d4,5) +
   B1[t] Ω4,1 + B2[t] Ω4,2 + B3[t] Ω4,3 + B4[t] Ω4,4 + B5[t] Ω4,5;
dM5 = -M5[t] q5 + (nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) *
       M5[t]/(denK + M5[t])) (-B1[t] d5,1 - B2[t] d5,2 - B3[t] d5,3 - B4[t] d5,4 - B5[t] d5,5) +
   B1[t] Ω5,1 + B2[t] Ω5,2 + B3[t] Ω5,3 + B4[t] Ω5,4 + B5[t] Ω5,5;

KK = 0.2;
cc = 0.05;
qq = 0.3;
dd = 0.00015;
OM = 1;
nu = 1500;
den = 2;
```

```
tmax = 10 000;
par = {
  κ1 → KK, κ2 → KK, κ3 → KK, κ4 → KK, κ5 → KK,

  c1,1 → cc Net[[1]][[1]], c1,2 → cc Net[[1]][[2]],
  c1,3 → cc Net[[1]][[3]], c1,4 → cc Net[[1]][[4]], c1,5 → cc Net[[1]][[5]],
  c2,1 → cc Net[[2]][[1]], c2,2 → cc Net[[2]][[2]], c2,3 → cc Net[[2]][[3]],
  c2,4 → cc Net[[2]][[4]], c2,5 → cc Net[[2]][[5]],
  c3,1 → cc Net[[3]][[1]], c3,2 → cc Net[[3]][[2]], c3,3 → cc Net[[3]][[3]],
  c3,4 → cc Net[[3]][[4]], c3,5 → cc Net[[3]][[5]],
  c4,1 → cc Net[[4]][[1]], c4,2 → cc  Net[[4]][[2]], c4,3 → cc  Net[[4]][[3]],
  c4,4 → cc  Net[[4]][[4]], c4,5 → cc  Net[[4]][[5]],
  c5,1 → cc  Net[[5]][[1]], c5,2 → cc Net[[5]][[2]], c5,3 → cc Net[[5]][[3]],
  c5,4 → cc Net[[5]][[4]], c5,5 → cc Net[[5]][[5]],

  q1 → qq, q2 → qq, q3 → qq, q4 → qq, q5 → qq,

  d1,1 → dd, d1,2 → dd, d1,3 → dd, d1,4 → dd, d1,5 → dd,
  d2,1 → dd, d2,2 → dd, d2,3 → dd, d2,4 → dd, d2,5 → dd,
  d3,1 → dd, d3,2 → dd, d3,3 → dd, d3,4 → dd, d3,5 → dd,
  d4,1 → dd, d4,2 → dd, d4,3 → dd, d4,4 → dd, d4,5 → dd,
  d5,1 → dd, d5,2 → dd, d5,3 → dd, d5,4 → dd, d5,5 → dd,

  Ω1,1 → OM Net[[1]][[1]], Ω1,2 → OM Net[[1]][[2]],
  Ω1,3 → OM Net[[1]][[3]], Ω1,4 → OM Net[[1]][[4]], Ω1,5 → OM Net[[1]][[5]],
  Ω2,1 → OM Net[[2]][[1]], Ω2,2 → OM Net[[2]][[2]], Ω2,3 → OM Net[[2]][[3]],
  Ω2,4 → OM Net[[2]][[4]], Ω2,5 → OM Net[[2]][[5]],
  Ω3,1 → OM Net[[3]][[1]], Ω3,2 → OM Net[[3]][[2]], Ω3,3 → OM Net[[3]][[3]],
  Ω3,4 → OM Net[[3]][[4]], Ω3,5 → OM Net[[3]][[5]],
  Ω4,1 → OM Net[[4]][[1]], Ω4,2 → OM Net[[4]][[2]], Ω4,3 → OM Net[[4]][[3]],
  Ω4,4 → OM Net[[4]][[4]], Ω4,5 → OM Net[[4]][[5]],
  Ω5,1 → OM Net[[5]][[1]], Ω5,2 → OM Net[[5]][[2]], Ω5,3 → OM Net[[5]][[3]],
  Ω5,4 → OM Net[[5]][[4]], Ω5,5 → OM Net[[5]][[5]],
  nuK → nu,
  denK → den


 };


B10 = 1500;
B20 = 1500;
B30 = 1500;
```

```
B40 = 1500;
B50 = 1500;
M10 = 10;
M20 = 10;
M30 = 10;
M40 = 10;
M50 = 10;


sol =
 NDSolve[
  {
    B1'[t] == dB1,
    B2'[t] == dB2,
    B3'[t] == dB3,
    B4'[t] == dB4,
    B5'[t] == dB5,

    M1'[t] == dM1,
    M2'[t] == dM2,
    M3'[t] == dM3,
    M4'[t] == dM4,
    M5'[t] == dM5,


    B1[0] == B10,
    B2[0] == B20,
    B3[0] == B30,
    B4[0] == B40,
    B5[0] == B50,
    M1[0] == M10,
    M2[0] == M20,
    M3[0] == M30,
    M4[0] == M40,
    M5[0] == M50

   } /. par,
  {B1, B2, B3, B4, B5, M1, M2, M3, M4, M5},
  {t, 0, tmax}];

Flatten[{B1[tmax], B2[tmax], B3[tmax], B4[tmax], B5[tmax],
    M1[tmax], M2[tmax], M3[tmax], M4[tmax], M5[tmax]} /. sol /. par]
```

```
)
```

As an example let's take the following Network

In[7379]:=
```
NetK = {
    {0, 1, 0, 1, 0},
    {1, 0, 1, 1, 0},
    {1, 0, 1, 0, 1},
    {0, 1, 0, 1, 0},
    {0, 0, 0, 0, 1}
   };
```

In[7421]:=
```
fNewSaitoKIC[NetK]
```

Out[7421]=
```
{6661.68, 6661.43, 6661.43, 6661.68,
 6661.93, 22 219.9, 44 425.5, 44 426.3, 22 219.9, 15.9422}
```

The function "fNewSaitoIC" solves the ODE system and receives a network and a initial conditions values as arguments.

In[7422]:=
```
fNewSaitoIC[Net_, IC_] := (

  dB1 =
   B1[t] (-B1[t] κ1 + nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) *
        M5[t]/(denK + M5[t])) - (c1,1 + c1,2 + c1,3 + c1,4 + c1,5) B1[t];
  dB2 = B2[t] (-B2[t] κ2 + nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) *
        M4[t]/(denK + M4[t]) * M5[t]/(denK + M5[t])) - (c2,1 + c2,2 + c2,3 + c2,4 + c2,5) B2[t];
  dB3 = B3[t] (-B3[t] κ3 + nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) *
        M4[t]/(denK + M4[t]) * M5[t]/(denK + M5[t])) - (c3,1 + c3,2 + c3,3 + c3,4 + c3,5) B3[t];
  dB4 = B4[t] (-B4[t] κ4 + nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) *
        M4[t]/(denK + M4[t]) * M5[t]/(denK + M5[t])) - (c4,1 + c4,2 + c4,3 + c4,4 + c4,5) B4[t];
  dB5 = B5[t] (-B5[t] κ5 + nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) *
```

```
        M4[t]/(denK + M4[t]) * M5[t]/(denK + M5[t])) - (c5,1 + c5,2 + c5,3 + c5,4 + c5,5) B5[t];

dM1 = -M1[t] q1 +
   (nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) * M5[t]/(denK + M5[t]))
    (-B1[t] d1,1 - B2[t] d1,2 - B3[t] d1,3 - B4[t] d1,4 - B5[t] d1,5) +
   B1[t] Ω1,1 + B2[t] Ω1,2 + B3[t] Ω1,3 + B4[t] Ω1,4 + B5[t] Ω1,5;
dM2 = -M2[t] q2 + (nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) *
      M5[t]/(denK + M5[t])) (-B1[t] d2,1 - B2[t] d2,2 - B3[t] d2,3 - B4[t] d2,4 - B5[t] d2,5) +
   B1[t] Ω2,1 + B2[t] Ω2,2 + B3[t] Ω2,3 + B4[t] Ω2,4 + B5[t] Ω2,5;
dM3 = -M3[t] q3 + (nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) *
      M5[t]/(denK + M5[t])) (-B1[t] d3,1 - B2[t] d3,2 - B3[t] d3,3 - B4[t] d3,4 - B5[t] d3,5) +
   B1[t] Ω3,1 + B2[t] Ω3,2 + B3[t] Ω3,3 + B4[t] Ω3,4 + B5[t] Ω3,5;
dM4 = -M4[t] q4 + (nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) *
      M5[t]/(denK + M5[t])) (-B1[t] d4,1 - B2[t] d4,2 - B3[t] d4,3 - B4[t] d4,4 - B5[t] d4,5) +
   B1[t] Ω4,1 + B2[t] Ω4,2 + B3[t] Ω4,3 + B4[t] Ω4,4 + B5[t] Ω4,5;
dM5 = -M5[t] q5 + (nuK * M1[t]/(denK + M1[t]) * M2[t]/(denK + M2[t]) * M3[t]/(denK + M3[t]) * M4[t]/(denK + M4[t]) *
      M5[t]/(denK + M5[t])) (-B1[t] d5,1 - B2[t] d5,2 - B3[t] d5,3 - B4[t] d5,4 - B5[t] d5,5) +
   B1[t] Ω5,1 + B2[t] Ω5,2 + B3[t] Ω5,3 + B4[t] Ω5,4 + B5[t] Ω5,5;

KK = 0.2;
cc = 0.05;
qq = 0.3;
dd = 0.00015;
OM = 1;
nu = 1500;
den = 2;

tmax = 10 000;
par = {
  κ1 → KK, κ2 → KK, κ3 → KK, κ4 → KK, κ5 → KK,

  c1,1 → cc Net[[1]][[1]], c1,2 → cc Net[[1]][[2]],
  c1,3 → cc Net[[1]][[3]], c1,4 → cc Net[[1]][[4]], c1,5 → cc Net[[1]][[5]],
  c2,1 → cc Net[[2]][[1]], c2,2 → cc Net[[2]][[2]], c2,3 → cc Net[[2]][[3]],
```

```
  c2,4 → cc Net[[2]][[4]], c2,5 → cc Net[[2]][[5]],
  c3,1 → cc Net[[3]][[1]], c3,2 → cc Net[[3]][[2]], c3,3 → cc Net[[3]][[3]],
  c3,4 → cc Net[[3]][[4]], c3,5 → cc Net[[3]][[5]],
  c4,1 → cc Net[[4]][[1]], c4,2 → cc  Net[[4]][[2]], c4,3 → cc  Net[[4]][[3]],
  c4,4 → cc  Net[[4]][[4]], c4,5 → cc  Net[[4]][[5]],
  c5,1 → cc  Net[[5]][[1]], c5,2 → cc Net[[5]][[2]], c5,3 → cc Net[[5]][[3]],
  c5,4 → cc Net[[5]][[4]], c5,5 → cc Net[[5]][[5]],

  q1 → qq, q2 → qq, q3 → qq, q4 → qq, q5 → qq,

  d1,1 → dd, d1,2 → dd, d1,3 → dd, d1,4 → dd, d1,5 → dd,
  d2,1 → dd, d2,2 → dd, d2,3 → dd, d2,4 → dd, d2,5 → dd,
  d3,1 → dd, d3,2 → dd, d3,3 → dd, d3,4 → dd, d3,5 → dd,
  d4,1 → dd, d4,2 → dd, d4,3 → dd, d4,4 → dd, d4,5 → dd,
  d5,1 → dd, d5,2 → dd, d5,3 → dd, d5,4 → dd, d5,5 → dd,

  Ω1,1 → OM Net[[1]][[1]], Ω1,2 → OM Net[[1]][[2]],
  Ω1,3 → OM Net[[1]][[3]], Ω1,4 → OM Net[[1]][[4]], Ω1,5 → OM Net[[1]][[5]],
  Ω2,1 → OM Net[[2]][[1]], Ω2,2 → OM Net[[2]][[2]], Ω2,3 → OM Net[[2]][[3]],
  Ω2,4 → OM Net[[2]][[4]], Ω2,5 → OM Net[[2]][[5]],
  Ω3,1 → OM Net[[3]][[1]], Ω3,2 → OM Net[[3]][[2]], Ω3,3 → OM Net[[3]][[3]],
  Ω3,4 → OM Net[[3]][[4]], Ω3,5 → OM Net[[3]][[5]],
  Ω4,1 → OM Net[[4]][[1]], Ω4,2 → OM Net[[4]][[2]], Ω4,3 → OM Net[[4]][[3]],
  Ω4,4 → OM Net[[4]][[4]], Ω4,5 → OM Net[[4]][[5]],
  Ω5,1 → OM Net[[5]][[1]], Ω5,2 → OM Net[[5]][[2]], Ω5,3 → OM Net[[5]][[3]],
  Ω5,4 → OM Net[[5]][[4]], Ω5,5 → OM Net[[5]][[5]],
  nuK → nu,
  denK → den


 };


B10 = IC[[1]];
B20 = IC[[2]];
B30 = IC[[3]];
B40 = IC[[4]];
B50 = IC[[5]];
M10 = IC[[6]];
M20 = IC[[7]];
M30 = IC[[8]];
M40 = IC[[9]];
M50 = IC[[10]];
```

```
sol =
 NDSolve[
  {
    B1'[t] == dB1,
    B2'[t] == dB2,
    B3'[t] == dB3,
    B4'[t] == dB4,
    B5'[t] == dB5,

    M1'[t] == dM1,
    M2'[t] == dM2,
    M3'[t] == dM3,
    M4'[t] == dM4,
    M5'[t] == dM5,


    B1[0] == B10,
    B2[0] == B20,
    B3[0] == B30,
    B4[0] == B40,
    B5[0] == B50,
    M1[0] == M10,
    M2[0] == M20,
    M3[0] == M30,
    M4[0] == M40,
    M5[0] == M50

   } /. par,
  {B1, B2, B3, B4, B5, M1, M2, M3, M4, M5},
  {t, 0, tmax}];

 Flatten[{B1[tmax], B2[tmax], B3[tmax], B4[tmax], B5[tmax],
    M1[tmax], M2[tmax], M3[tmax], M4[tmax], M5[tmax]} /. sol /. par]
```

In[7423]:=
```
NetK = {
    {0, 1, 0, 1, 0},
    {1, 0, 1, 1, 0},
    {1, 0, 1, 0, 1},
    {0, 1, 0, 1, 0},
    {0, 0, 0, 0, 1}
   };
```

The function “fNewSaitoKIC” solves the ODE system and gives the population at steady state of the system, starting with arbitrary initial conditions.

In[7424]:=
```
IC1 = fNewSaitoKIC[NetK]
```

Out[7424]=
```
{6661.68, 6661.43, 6661.43, 6661.68,
 6661.93, 22 219.9, 44 425.5, 44 426.3, 22 219.9, 15.9422}
```

We create now two vectors that increase 50 fold one (“OneMetHigh”) or all (“AllMetHigh”) metabolites

In[7425]:=
```
OneMetHigh = {1, 1, 1, 1, 1, 50, 1, 1, 1, 1};
```

In[7426]:=
```
AllMetHigh = {1, 1, 1, 1, 1, 50, 50, 50, 50, 50};
```

This results in the following initial conditions when one metabolite is increased:

In[7427]:=
```
fNewSaitoKIC[NetK] OneMetHigh
```

Out[7427]=
```
{6661.68, 6661.43, 6661.43, 6661.68, 6661.93,
 1.11099 × 10^6, 44 425.5, 44 426.3, 22 219.9, 15.9422}
```

We provide the new initial condition as an argument in the function “fNewSaitoIC”:

In[7428]:=
```
IC2 = fNewSaitoIC[NetK, fNewSaitoKIC[NetK] OneMetHigh]
```

Out[7428]=
```
{6661.68, 6661.43, 6661.43, 6661.68,
 6661.93, 22 219.9, 44 425.5, 44 426.3, 22 219.9, 15.9422}
```

We see that the system converges to the initial state:

In[7429]:=
```
IC1 == IC2
```
Out[7429]=
```
True
```

This results in the following initial conditions when all metabolites are increased:

In[7430]:=
```
fNewSaitoKIC[NetK] AllMetHigh
```
Out[7430]=
$$\{6661.68, 6661.43, 6661.43, 6661.68, 6661.93, 1.11099 \times 10^6, 2.22127 \times 10^6, 2.22132 \times 10^6, 1.11099 \times 10^6, 797.108\}$$

We provide the new initial condition as an argument in the function “fNewSaitoIC”:

In[7431]:=
```
IC3 = fNewSaitoIC[NetK, fNewSaitoKIC[NetK] AllMetHigh]
```
Out[7431]=
```
{6661.68, 6661.43, 6661.43, 6661.68,
 6661.93, 22 219.9, 44 425.5, 44 426.3, 22 219.9, 15.9422}
```

We see that the system converges to the initial state:

In[7432]:=
```
IC1 == IC3
```
Out[7432]=
```
True
```

We now systematically analyse all networks with 8 auxotrophies, as an example:

In[7395]:=
```
hk8
```

In[7433]:=
```
ICList1 = Parallelize[fNewSaitoKIC /@ hk8]
```

In[7434]:=
```
ICList1[[1]]
```
Out[7434]=
```
{7497.06, 7497.31, 7497.56, 7497.81,
 7497.56, 96 848.5, 71 857.5, 46 865.6, 21 872.1, 46 864.8}
```

In[7435]:=
```
ICList2 = Parallelize[
  fNewSaitoIC[hk8[[#]], fNewSaitoKIC[hk8[[#]]] OneMetHigh] & /@ Range[100]]
```

In[7438]:=
```
ICList1 == ICList2
```

Out[7438]= True

In[7439]:=
```
ICList3 = Parallelize[
  fNewSaitoIC[hk8[[#]], fNewSaitoKIC[hk8[[#]]] AllMetHigh] & /@ Range[100]]
```

In[7441]:=
```
ICList1 == ICList3
```

Out[7441]= True

We can then conclude that the system is stable for changes in the initial conditions of one or all metabolites.