

```
<< mathsbml.m
```

```
MathSBML 2.2.1-beta-17 (25-Feb-2004) loaded 27-February-2004 22:00:46.515673
```

Mitotic Oscillator

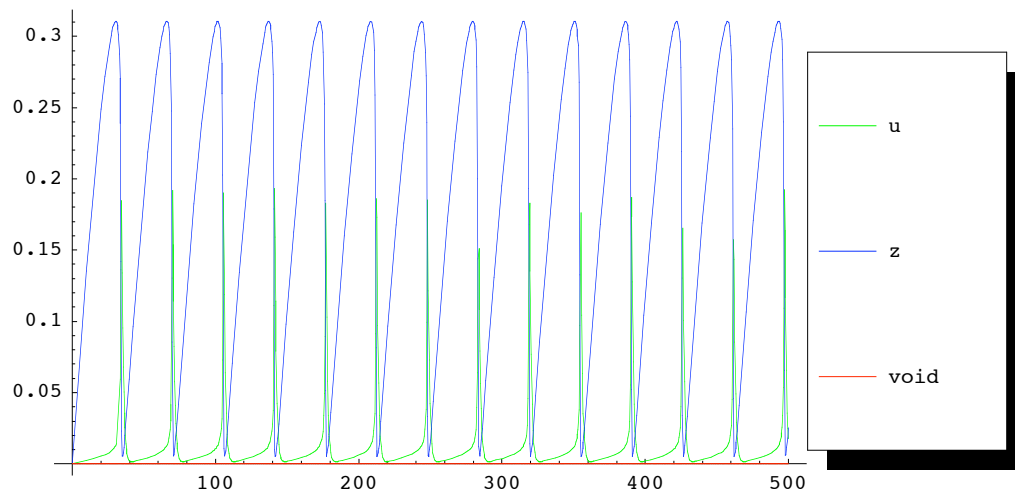
Based on the two-variable model in
Tyson, J.J. (1991) Modeling the cell division cycle: cdc2 and
cyclin interactions. Proc. Natl. Acad. Sci., USA, 88:7328-7332

- 1 Create the basic model without cell division and plot
2. Solve for fixed point of the system and calculate eigenvalues
3. Examine fixed point as a function of parameters
4. Create model with event-triggered cell division
5. Run Simulation with an event
6. Plot the simulation showing cell division (event action)

Create a Model without the event with the Model Builder

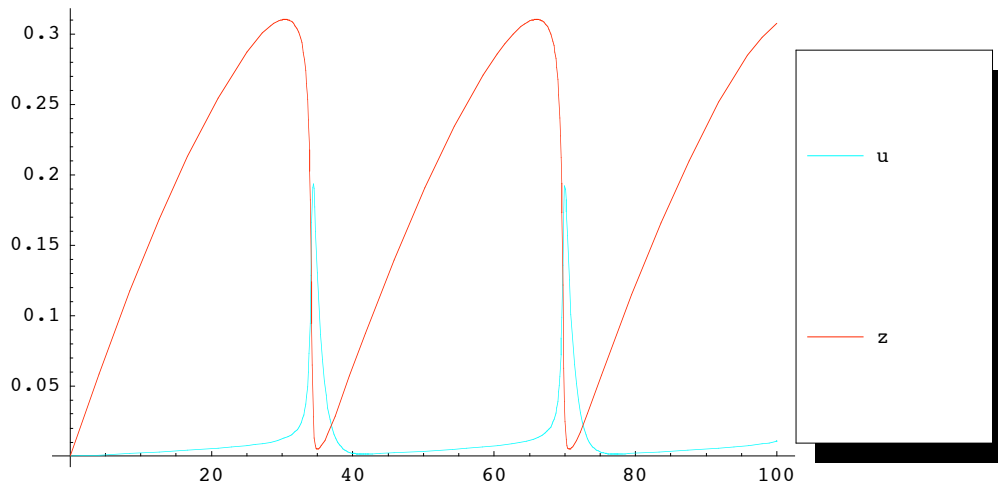
```
newModel[id → "MO", name → "Mitotic Oscillator with Events [Tyson 1991]", echo → False];
addSpecies[{u, z}, initialAmount → 0];
addSpecies[void, boundaryCondition → True, initialAmount → 0];
addReaction[void → z, kineticLaw → k, parameters → {k → 0.015}];
addReaction[u → void, kineticLaw → k6 * u, parameters → {k6 → 1}];
addReaction[z → u, kineticLaw → k4 * z * (k4prime / k4 + u^2),
  parameters → {k4 → 180, k4prime → 0.018}];
m = loadSimulator[];
s = SBMLNDSolve[m, 500];
SBMLPlot[s, PlotRange → All];
```

>>Warning: The following variable(s) do(es) not have differential equations:
void[t]; the following odes have been added to the system: void'[t] == 0



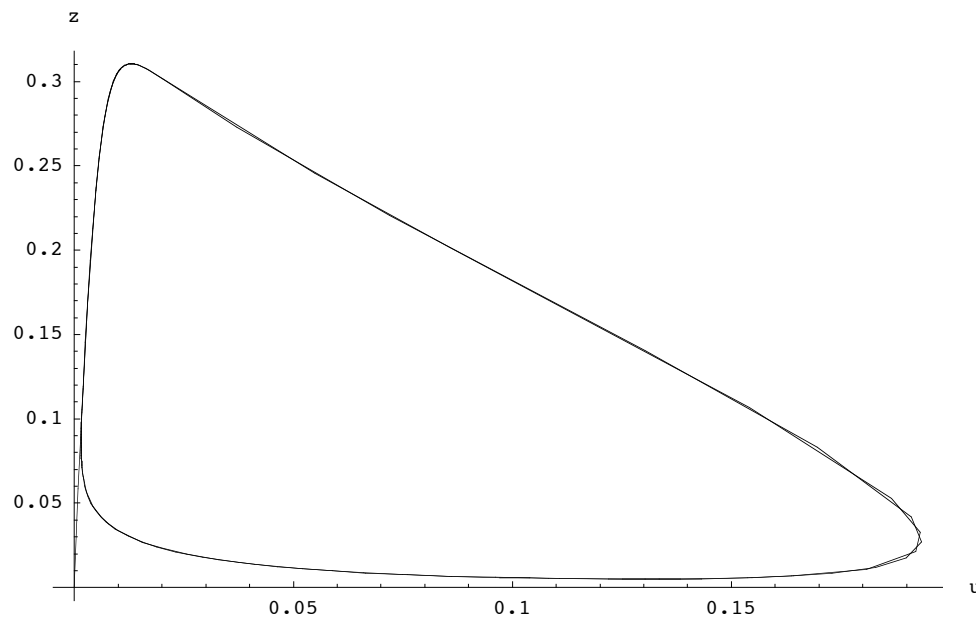
- The model has two variables; we will treat the "spikey" variable u as a variable that must pass a threshold for the cell to divide

```
SBMLPlot[s, {MO`u, MO`z}, {0, 100}]
```



- Graphics -

```
ParametricPlot[Evaluate[{MO`u[t], MO`z[t]} /. s], {t, 0, 100}, AxesLabel -> {"u", "z"}];
```



Solve for fixed point of the system

```
q = loadSimulator[context -> None];
```

```
odes = SBMLODES /. q
{u'[t] == -1. u[t] + 180. (0.0001 + u[t]^2) z[t], z'[t] == 0.015 - 180. (0.0001 + u[t]^2) z[t]}
{z0, u0} = Flatten[{z[t], u[t]} /. (Solve[({# == 0 &} /@Last /@odes, {u[t], z[t]})]]]
{0.25641, 0.015}
```

■ Find the Jacobian

```
{f, g} = Last /@ (odes /. {u[t] → u, z[t] → z})
{-1. u + 180. (0.0001 + u^2) z, 0.015 - 180. (0.0001 + u^2) z}
J = ( D[f, u] D[f, z]
      D[g, u] D[g, z] ); MatrixForm[J]
( -1. + 360. u z   180. (0.0001 + u^2)
  -360. u z      -180. (0.0001 + u^2) )
```

■ Find the eigenvalues of the Jacobian

```
eigenvalues = Solve[Det[J - λ I] == 0, λ] // Flatten
{λ →  $\frac{-0.018 - 180. u^2 + 0. u z + 0. u^3 z}{(0. + 1.036 i) + (0. + 360. i) u^2 - (0. + 720. i) u z}$ }
```

■ The eigenvalues at the fixed point are purely imaginary

```
eigenvalues /. {u → u0, z → z0}
{λ → 0. - 0.0354067 i}
```

Examine the Fixed point as a function of the parameters

■ Create model without values for the parameters and then solve for fixed point as a function of the parameter names

```
newModel[id → "MO", name → "Mitotic Oscillator with Events [Tyson 1991]", echo → False];
addSpecies[{u, z}, initialAmount → 0];
addSpecies[void, boundaryCondition → True, initialAmount → 0];
addReaction[void → z, kineticLaw → k];
addReaction[u → void, kineticLaw → k6 * u];
addReaction[z → u, kineticLaw → k4 * z * (k4prime / k4 + u^2)];
q = loadSimulator[context → None];
odes = SBMLODES /. q
{u'[t] == -k6 u[t] + k4 (  $\frac{k4prime}{k4} + u[t]^2$  ) z[t], z'[t] == k - k4 (  $\frac{k4prime}{k4} + u[t]^2$  ) z[t]}
```

```
fixedPoint = Solve[ (# == 0 &) /@ Last /@ odes, {u[t], z[t]}]
```

$$\left\{ \left\{ z[t] \rightarrow \frac{k k6^2}{k^2 k4 + k4prime k6^2}, u[t] \rightarrow \frac{k}{k6} \right\} \right\}$$

■ Fixed Point

```
{z0, u0} = Flatten[{z[t], u[t]} /. fixedPoint]
```

$$\left\{ \frac{k k6^2}{k^2 k4 + k4prime k6^2}, \frac{k}{k6} \right\}$$

```
{f, g} = Last /@ (odes /. {u[t] -> u, z[t] -> z})
```

$$\left\{ -k6 u + k4 \left(\frac{k4prime}{k4} + u^2 \right) z, k - k4 \left(\frac{k4prime}{k4} + u^2 \right) z \right\}$$

■ Calculate Jacobian

```
J = ( D[f, u] D[f, z] ); MatrixForm[J]
```

$$\begin{pmatrix} -k6 + 2 k4 u z & k4 \left(\frac{k4prime}{k4} + u^2 \right) \\ -2 k4 u z & -k4 \left(\frac{k4prime}{k4} + u^2 \right) \end{pmatrix}$$

■ Find the eigenvalues of the Jacobian

```
eigenvalues = Solve[Det[J - λ I] == 0, λ] // Flatten
```

$$\left\{ \lambda \rightarrow \frac{i (k4prime k6 + k4 k6 u^2)}{2 k4prime + k6 + 2 k4 u^2 - 4 k4 u z} \right\}$$

■ Find a formula for the eigenvalues at the fixed point as a function of the parameters

```
eigenvalues /. {u -> u0, z -> z0} // Simplify
```

$$\left\{ \lambda \rightarrow \frac{i k6 (k^2 k4 + k4prime k6^2)^2}{2 k^4 k4^2 + k^2 k4 (4 k4prime - 3 k6) k6^2 + k4prime k6^4 (2 k4prime + k6)} \right\}$$

Add cell division to the model - add mass that divides on a threshold

- mass grows exponentially;
- event: if mass > threshold AND protein u > threshold, divide cell in half: mass -> mass/2

```
newModel[id → "MO", name → "Mitotic Oscillator with Events [Tyson 1991]", echo → False];
addSpecies[{u, z}, initialAmount → 0];
addSpecies[void, boundaryCondition → True, initialAmount → 0];
addParameter[cellmass, value → 0.25, constant → False];
addReaction[void → z, kineticLaw → k, parameters → {k → 0.015}];
addReaction[u → void, kineticLaw → k6 * u, parameters → {k6 → 1}];
addReaction[z → u, kineticLaw → k4 * z * (k4prime / k4 + u^2),
  parameters → {k4 → 180, k4prime → 0.018}];
addRule[type → "rateRule", variable → cellmass, math → 0.035 * cellmass];
addEvent[id → "cellDivision", trigger → ((cellmass > 0.75) && (u > 0.175)),
  eventAssignment → {cellmass → cellmass / 2}];
createModel["MO.xml"]
```

MO.xml

Load the model into the simulate and run a simulation

```
m = loadSimulator[];
s = SBMLNDSolve[m, 500]
```

```
>>Warning: The following variable(s) do(es) not have differential equations:
void[t]; the following odes have been added to the system: void'[t] == 0
```

```
{InterpolationSet[0, 34.2473, {MO`u[t] → InterpolatingFunction[{{0., 34.2588}}, <>][t],
  MO`z[t] → InterpolatingFunction[{{0., 34.2588}}, <>][t],
  MO`void[t] → InterpolatingFunction[{{0., 34.2588}}, <>][t],
  MO`cellmass[t] → InterpolatingFunction[{{0., 34.2588}}, <>][t]}, InterpolationSet[
  34.2473, 69.8452, {MO`u[t] → InterpolatingFunction[{{34.2473, 69.8575}}, <>][t],
  MO`z[t] → InterpolatingFunction[{{34.2473, 69.8575}}, <>][t],
  MO`void[t] → InterpolatingFunction[{{34.2473, 69.8575}}, <>][t],
  MO`cellmass[t] → InterpolatingFunction[{{34.2473, 69.8575}}, <>][t]},
  InterpolationSet[69.8452, 105.443,
  {MO`u[t] → InterpolatingFunction[{{69.8452, 105.455}}, <>][t],
  MO`z[t] → InterpolatingFunction[{{69.8452, 105.455}}, <>][t],
  MO`void[t] → InterpolatingFunction[{{69.8452, 105.455}}, <>][t],
  MO`cellmass[t] → InterpolatingFunction[{{69.8452, 105.455}}, <>][t]},
  InterpolationSet[105.443, 105.443,
  {MO`u[t] → InterpolatingFunction[{{105.443, 105.443}}, <>][t],
  MO`z[t] → InterpolatingFunction[{{105.443, 105.443}}, <>][t],
  MO`void[t] → InterpolatingFunction[{{105.443, 105.443}}, <>][t],
  MO`cellmass[t] → InterpolatingFunction[{{105.443, 105.443}}, <>][t]},
  InterpolationSet[105.443, 141.041,
  {MO`u[t] → InterpolatingFunction[{{105.443, 141.053}}, <>][t],
```

```

MO`z[t] → InterpolatingFunction[{{105.443, 141.053}}, <>][t],
MO`void[t] → InterpolatingFunction[{{105.443, 141.053}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{105.443, 141.053}}, <>][t]],
InterpolationSet[141.041, 141.041,
{MO`u[t] → InterpolatingFunction[{{141.041, 141.041}}, <>][t],
MO`z[t] → InterpolatingFunction[{{141.041, 141.041}}, <>][t],
MO`void[t] → InterpolatingFunction[{{141.041, 141.041}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{141.041, 141.041}}, <>][t]]},
InterpolationSet[141.041, 176.639,
{MO`u[t] → InterpolatingFunction[{{141.041, 176.651}}, <>][t],
MO`z[t] → InterpolatingFunction[{{141.041, 176.651}}, <>][t],
MO`void[t] → InterpolatingFunction[{{141.041, 176.651}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{141.041, 176.651}}, <>][t]]},
InterpolationSet[176.639, 176.639,
{MO`u[t] → InterpolatingFunction[{{176.639, 176.639}}, <>][t],
MO`z[t] → InterpolatingFunction[{{176.639, 176.639}}, <>][t],
MO`void[t] → InterpolatingFunction[{{176.639, 176.639}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{176.639, 176.639}}, <>][t]]},
InterpolationSet[176.639, 212.237,
{MO`u[t] → InterpolatingFunction[{{176.639, 212.249}}, <>][t],
MO`z[t] → InterpolatingFunction[{{176.639, 212.249}}, <>][t],
MO`void[t] → InterpolatingFunction[{{176.639, 212.249}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{176.639, 212.249}}, <>][t]]},
InterpolationSet[212.237, 212.237,
{MO`u[t] → InterpolatingFunction[{{212.237, 212.237}}, <>][t],
MO`z[t] → InterpolatingFunction[{{212.237, 212.237}}, <>][t],
MO`void[t] → InterpolatingFunction[{{212.237, 212.237}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{212.237, 212.237}}, <>][t]]},
InterpolationSet[212.237, 247.835,
{MO`u[t] → InterpolatingFunction[{{212.237, 247.847}}, <>][t],
MO`z[t] → InterpolatingFunction[{{212.237, 247.847}}, <>][t],
MO`void[t] → InterpolatingFunction[{{212.237, 247.847}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{212.237, 247.847}}, <>][t]]},
InterpolationSet[247.835, 283.433,
{MO`u[t] → InterpolatingFunction[{{247.835, 283.445}}, <>][t],
MO`z[t] → InterpolatingFunction[{{247.835, 283.445}}, <>][t],
MO`void[t] → InterpolatingFunction[{{247.835, 283.445}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{247.835, 283.445}}, <>][t]]},
InterpolationSet[283.433, 283.433,
{MO`u[t] → InterpolatingFunction[{{283.433, 283.433}}, <>][t],
MO`z[t] → InterpolatingFunction[{{283.433, 283.433}}, <>][t],
MO`void[t] → InterpolatingFunction[{{283.433, 283.433}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{283.433, 283.433}}, <>][t]]},
InterpolationSet[283.433, 319.031,
{MO`u[t] → InterpolatingFunction[{{283.433, 319.043}}, <>][t],
MO`z[t] → InterpolatingFunction[{{283.433, 319.043}}, <>][t],
MO`void[t] → InterpolatingFunction[{{283.433, 319.043}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{283.433, 319.043}}, <>][t]]},
InterpolationSet[319.031, 319.031,
{MO`u[t] → InterpolatingFunction[{{319.031, 319.031}}, <>][t],
MO`z[t] → InterpolatingFunction[{{319.031, 319.031}}, <>][t],
MO`void[t] → InterpolatingFunction[{{319.031, 319.031}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{319.031, 319.031}}, <>][t]]},
InterpolationSet[319.031, 354.628,
{MO`u[t] → InterpolatingFunction[{{319.031, 354.641}}, <>][t],
MO`z[t] → InterpolatingFunction[{{319.031, 354.641}}, <>][t],
MO`void[t] → InterpolatingFunction[{{319.031, 354.641}}, <>][t],
MO`cellmass[t] → InterpolatingFunction[{{319.031, 354.641}}, <>][t]]},

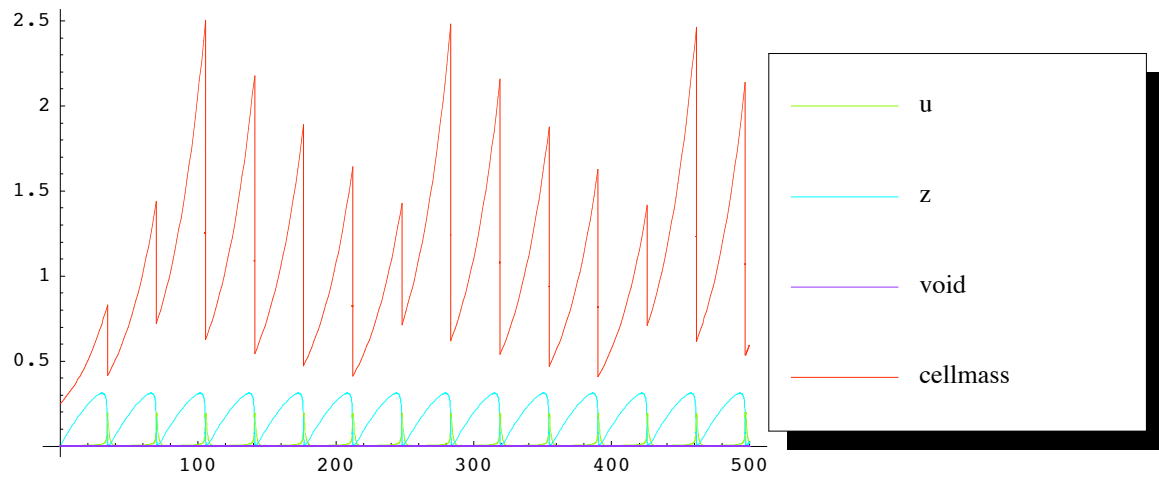
```

```

InterpolationSet[354.628, 354.628,
  {MO`u[t] → InterpolatingFunction[{{354.628, 354.629}}, <>][t],
   MO`z[t] → InterpolatingFunction[{{354.628, 354.629}}, <>][t],
   MO`void[t] → InterpolatingFunction[{{354.628, 354.629}}, <>][t],
   MO`cellmass[t] → InterpolatingFunction[{{354.628, 354.629}}, <>][t]}],
InterpolationSet[354.628, 390.226,
  {MO`u[t] → InterpolatingFunction[{{354.628, 390.239}}, <>][t],
   MO`z[t] → InterpolatingFunction[{{354.628, 390.239}}, <>][t],
   MO`void[t] → InterpolatingFunction[{{354.628, 390.239}}, <>][t],
   MO`cellmass[t] → InterpolatingFunction[{{354.628, 390.239}}, <>][t]}],
InterpolationSet[390.226, 390.226,
  {MO`u[t] → InterpolatingFunction[{{390.226, 390.226}}, <>][t],
   MO`z[t] → InterpolatingFunction[{{390.226, 390.226}}, <>][t],
   MO`void[t] → InterpolatingFunction[{{390.226, 390.226}}, <>][t],
   MO`cellmass[t] → InterpolatingFunction[{{390.226, 390.226}}, <>][t]}],
InterpolationSet[390.226, 425.824,
  {MO`u[t] → InterpolatingFunction[{{390.226, 425.837}}, <>][t],
   MO`z[t] → InterpolatingFunction[{{390.226, 425.837}}, <>][t],
   MO`void[t] → InterpolatingFunction[{{390.226, 425.837}}, <>][t],
   MO`cellmass[t] → InterpolatingFunction[{{390.226, 425.837}}, <>][t]}],
InterpolationSet[425.824, 461.422,
  {MO`u[t] → InterpolatingFunction[{{425.824, 461.434}}, <>][t],
   MO`z[t] → InterpolatingFunction[{{425.824, 461.434}}, <>][t],
   MO`void[t] → InterpolatingFunction[{{425.824, 461.434}}, <>][t],
   MO`cellmass[t] → InterpolatingFunction[{{425.824, 461.434}}, <>][t]}],
InterpolationSet[461.422, 461.422,
  {MO`u[t] → InterpolatingFunction[{{461.422, 461.422}}, <>][t],
   MO`z[t] → InterpolatingFunction[{{461.422, 461.422}}, <>][t],
   MO`void[t] → InterpolatingFunction[{{461.422, 461.422}}, <>][t],
   MO`cellmass[t] → InterpolatingFunction[{{461.422, 461.422}}, <>][t]}],
InterpolationSet[461.422, 497.02,
  {MO`u[t] → InterpolatingFunction[{{461.422, 497.032}}, <>][t],
   MO`z[t] → InterpolatingFunction[{{461.422, 497.032}}, <>][t],
   MO`void[t] → InterpolatingFunction[{{461.422, 497.032}}, <>][t],
   MO`cellmass[t] → InterpolatingFunction[{{461.422, 497.032}}, <>][t]}],
InterpolationSet[497.02, 497.02,
  {MO`u[t] → InterpolatingFunction[{{497.02, 497.02}}, <>][t],
   MO`z[t] → InterpolatingFunction[{{497.02, 497.02}}, <>][t],
   MO`void[t] → InterpolatingFunction[{{497.02, 497.02}}, <>][t],
   MO`cellmass[t] → InterpolatingFunction[{{497.02, 497.02}}, <>][t]}], InterpolationSet[
497.02, 500., {MO`u[t] → InterpolatingFunction[{{497.02, 500.}}, <>][t],
  MO`z[t] → InterpolatingFunction[{{497.02, 500.}}, <>][t],
  MO`void[t] → InterpolatingFunction[{{497.02, 500.}}, <>][t],
  MO`cellmass[t] → InterpolatingFunction[{{497.02, 500.}}, <>][t]}]}

```

SBMLPlot[s]



- Graphics -

```
SBMLWrite[inputfile → "MO.xml", outputfile → "MO.html", format → "HTML"]
```

MO.html