Mathematical Modelling and Scientific Computing in the Biosciences

Lecture location: HF 9904, time: Tuesdays 13:45−15:15. Computer Lab: HF 107.
Lecturer: Dr. James Lu (Email: james.lu@oeaw.ac.at, Office: HF130)
Useful books:

- *"Computational Cell Biology", C. P. Fall, E. S. Marland, J. M. Wagner, J. J. Tyson, editors. Mathematical Biology Series, 2002, Springer Verlag.*
- *"An Introduction to Systems Biology: Design Principles of Biological Circuits", U. Alon, Mathematical and Computational Biology Series, 2007, CRC Press.*
- *"Mathematical Biology I: an Introduction", J. D. Murray. Mathematical Biology Series, 2002, Springer Verlag.*

Course Overview

Biological Topics/Models

- **Enzyme Kinetics**
  - **Mass−action, Hill−Langmuir equation, Michaelis−Menton equation**
- **Neuron Dynamics**
  - **Hodgkin−Huxley model**
- **Cell Cycle**
- **Circadian Rhythm**

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Course Overview

Mathematical Topics

- **Singular Perturbation**
  - **Fast/slow time−scale separation, Hill equation**
- **Non−Dimensionalization**
  - **Buckingham Π−theorem**
- **Numerical ODE integration**
  - **Methods, accuracy, stability**
- **Dynamical Systems**
  - **Bifurcations: theory and numerics**
- **Inverse Problems**
  - **Parameter identification, inverse dynamical analysis**

Course Overview

Computational Tools

- **MathSBML**

  − *Mathematica* package for reading and analysis of models encoded in the Systems Biology Markup−Language (SBML) format
  − Webpage: http://sbml.org/software/mathsbml/

- **MATCONT**

  − MATLAB package for bifurcation analysis of dynamical systems
  − Webpage: http://www.matcont.ugent.be/

- **SBML ODE Solver Library**

  − C library and command line application for numeric and symbolic analysis of SBML models
  − Webpage: http://www.tbi.univie.ac.at/~raim/odeSolver/

- **SBML Inverse Eigenvalue Analyzer**

– *Mathematica* Add–On package for exploring possibility of qualitative dynamical behaviors via inverse eigenvalue analysis

Illustrative Example: Hodgkin–Huxley Model of the Squid Axon

```
In[1]:= << MathSBML.m

     MathSBML Version 2.6.0.13 (21-Dec-2006) using Mathematica
       Version 5.2 for Linux (June 20, 2005) loaded 6-March-2007 08:08:30.064535

In[2]:= ModelHH = SBMLRead["~/Teaching/SBMLModels/HodgkinHuxley_Squid_Axon.xml", verbose → True, evaluateParameters → False];
```

File Name:~/Teaching/SBMLModels/HodgkinHuxley_Squid_Axon.xml
SBML Level 2 Version 1

Model name: hodgkin–huxley squid–axon 1952
Model id: hhsa_1952

Function Definitions

––––– None –––––

Unit Definitions (Excluding Built–in Units)

ID	MetaID	Name	Formula
time	metaid_0000003	⋯	second/1000
millisecond	metaid_0000004	⋯	second/1000
per_millisecond	metaid_0000005	⋯	1000/second
millivolt	metaid_0000006	⋯	volt/1000
milliS_per_cm2	metaid_0000007	⋯	(10*siemens)/metre^2
microF_per_cm2	metaid_0000008	⋯	farad/(100*metre^2)
microA_per_cm2	metaid_0000009	⋯	ampere/(100*metre^2)

Compartments

ID	MetaID	Name	Dimension	Size	Units	Derived Units	Outsi
default	⋯	⋯	3	⋯	volume	litre	⋯
unit_compartment	metaid_0000032	unit_compartment	3	⋯	volume	litre	defaul

Species

––––– None –––––

Global Parameters

ID	MetaID	Name	Value	Units	Derived Units
V	metaid_0000010	transmembrane voltage	−75	millivolt	volt/1000
II	metaid_0000011	applied current	0	microA_per_cm2	ampere/(100*metre^
i_Na	metaid_0000012	sodium current	…	microA_per_cm2	ampere/(100*metre^
i_K	metaid_0000013	potassium current	…	microA_per_cm2	ampere/(100*metre^
i_L	metaid_0000014	leakage current	…	microA_per_cm2	ampere/(100*metre^
m	metaid_0000015	sodium channel activation coefficient	0.05	dimensionless	dimensionless
h	metaid_0000016	sodium channel inactivation coefficient	0.6	dimensionless	dimensionless
n	metaid_0000017	potassium channel activation coefficient	0.325	dimensionless	dimensionless
E_R	metaid_0000018	resting membrane potential	−65	millivolt	volt/1000
Cm	metaid_0000019	membrane capacitance	1	microF_per_cm2	farad/(100*metre^2
g_Na	metaid_0000020	maximum sodium channel conductance	120	milliS_per_cm2	(10*siemens)/metre
g_K	metaid_0000021	maximum potassium channel conductance	36	milliS_per_cm2	(10*siemens)/metre
g_L	metaid_0000022	maximum leakage conductance	0.3	milliS_per_cm2	(10*siemens)/metre
E_Na	metaid_0000023	sodium equilibrium potential	…	millivolt	volt/1000
E_K	metaid_0000024	potassium equilibrium potential	…	millivolt	volt/1000
E_L	metaid_0000025	leakage equilibrium potential	…	millivolt	volt/1000
alpha_m	metaid_0000026	auxiliary alpha_m	…	per_millisecond	1000/second
beta_m	metaid_0000027	auxiliary beta_m	…	per_millisecond	1000/second
alpha_h	metaid_0000028	auxiliary alpha_h	…	per_millisecond	1000/second
beta_h	metaid_0000029	auxiliary beta_h	…	per_millisecond	1000/second
alpha_n	metaid_0000030	auxiliary alpha_n	…	per_millisecond	1000/second
beta_n	metaid_0000031	auxiliary beta_n	…	per_millisecond	1000/second

Rules

Metaid	Type	Formula
metaid_0000033	assignmentRule	E_Na[t]==115 + E_R
metaid_0000034	assignmentRule	E_K[t]==-12 + E_R
metaid_0000035	assignmentRule	E_L[t]==11 + E_R
metaid_0000036	assignmentRule	alpha_m[t]==(0.1*(40 + V[t]))/(1 - E^(-0.1*(40 + V[t])))
metaid_0000037	assignmentRule	beta_m[t]==4*E^((-65 - V[t])/18)
metaid_0000038	assignmentRule	alpha_h[t]==0.07*E^((-65 - V[t])/20)
metaid_0000039	assignmentRule	beta_h[t]==(1 + E^(-0.1*(35 + V[t])))^(-1)
metaid_0000040	assignmentRule	alpha_n[t]==(0.01*(55 + V[t]))/(1 - E^(-0.1*(55 + V[t])))
metaid_0000041	assignmentRule	beta_n[t]==0.125*E^((-65 - V[t])/80)
metaid_0000045	rateRule	m'[t]==alpha_m[t]*(1 - m[t]) - beta_m[t]*m[t]
metaid_0000046	rateRule	h'[t]==alpha_h[t]*(1 - h[t]) - beta_h[t]*h[t]
metaid_0000047	rateRule	n'[t]==alpha_n[t]*(1 - n[t]) - beta_n[t]*n[t]
metaid_0000042	assignmentRule	i_Na[t]==g_Na*h[t]*m[t]^3*(-E_Na[t] + V[t])
metaid_0000043	assignmentRule	i_K[t]==g_K*n[t]^4*(-E_K[t] + V[t])
metaid_0000044	assignmentRule	i_L[t]==g_L*(-E_L[t] + V[t])
metaid_0000048	rateRule	V'[t]==(II - i_K[t] - i_L[t] - i_Na[t])/Cm

Reactions

----- None -----

Events

----- None -----

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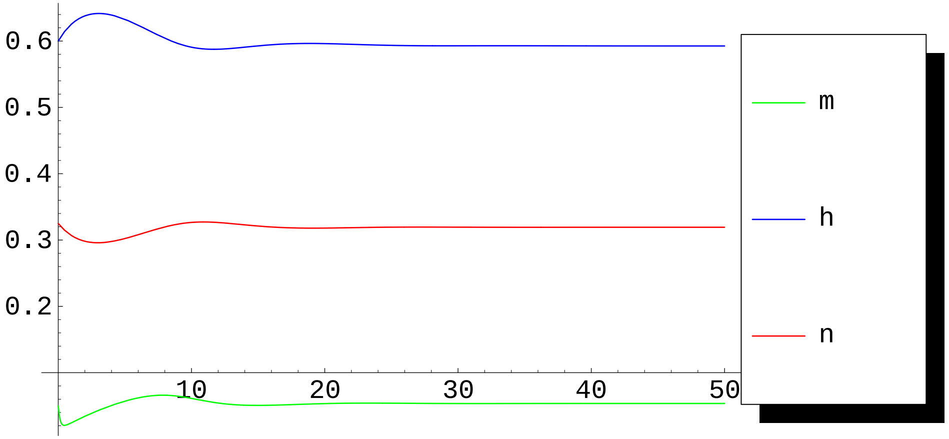
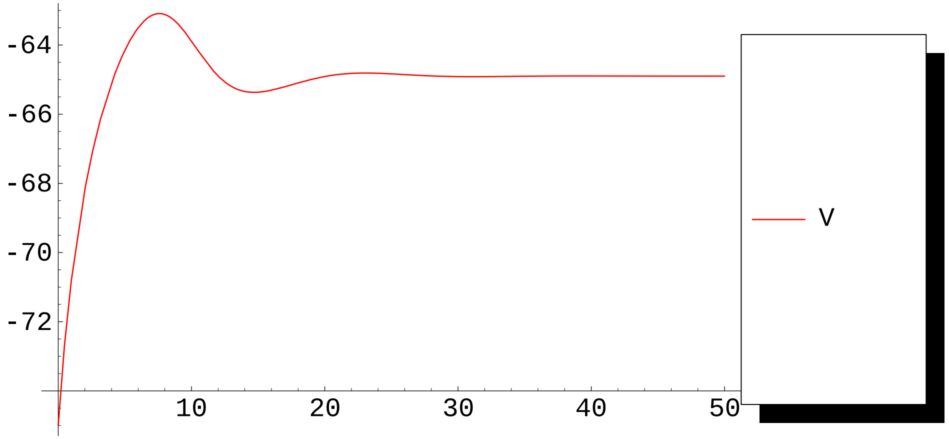
Simulating Time−Course: Hodgkin−Huxley model

```
In[15]:= SolnHH = SBMLNDSolve[ModelHH, 50];
         SBMLPlot[SolnHH, {m, h, n}, PlotRange → All, ImageSize → {450, 180}];
         VPlot1 = SBMLPlot[SolnHH, {V}, PlotRange → All, ImageSize → {450, 180}];
```



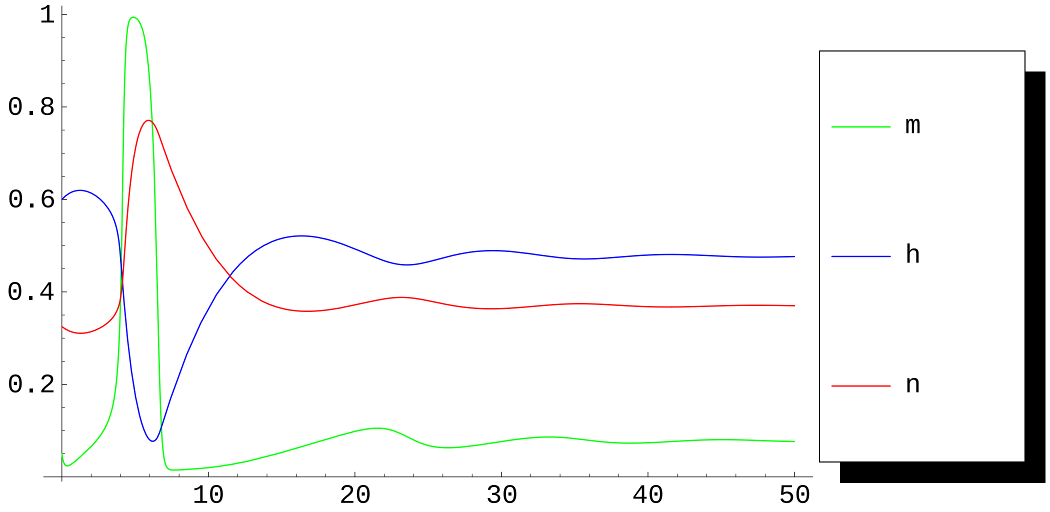


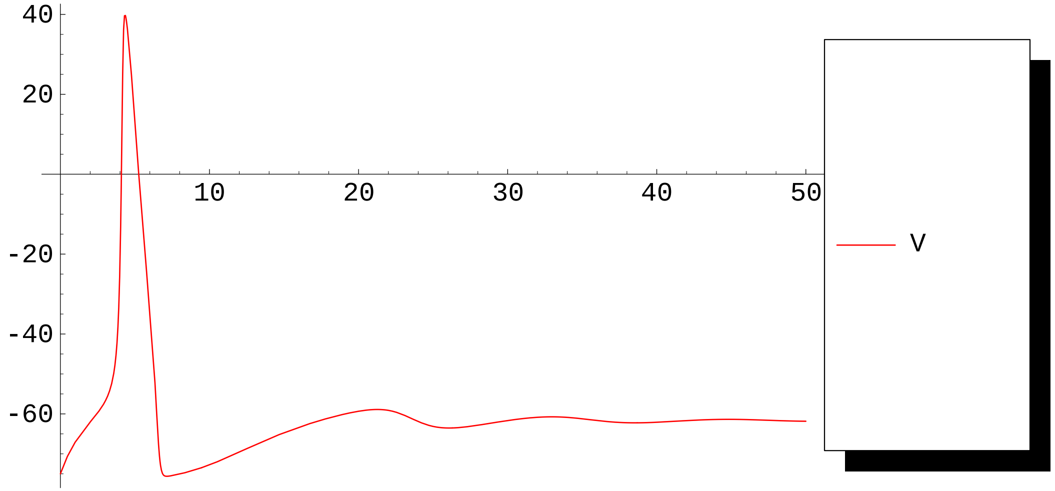
In[6]:= **ConstantsHH = SBMLConstants /. ModelHH**

Out[6]= {hhsa_1952'II → 0, hhsa_1952'E_R → -65, hhsa_1952'Cm → 1, hhsa_1952'g_Na → 120, hhsa_1952'g_K → 36, hhsa_1952'g_L → 0.3}

Effect of Applied Current in the Hodgkin−Huxley model

```
In[18]:= NewModelHH = resetParameter[ModelHH, {II → 5}];
         NewSolnHH = SBMLNDSolve[NewModelHH, 50];
         SBMLPlot[NewSolnHH, {m, h, n}, PlotRange → All, ImageSize → {450, 200}];
         VPlot2 = SBMLPlot[NewSolnHH, {V}, PlotRange → All, ImageSize → {450, 200}];
```





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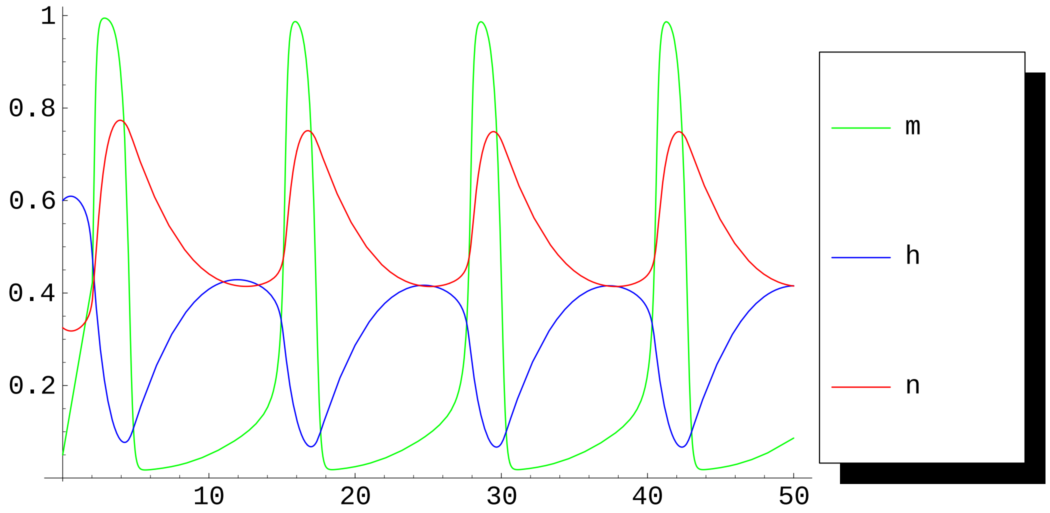
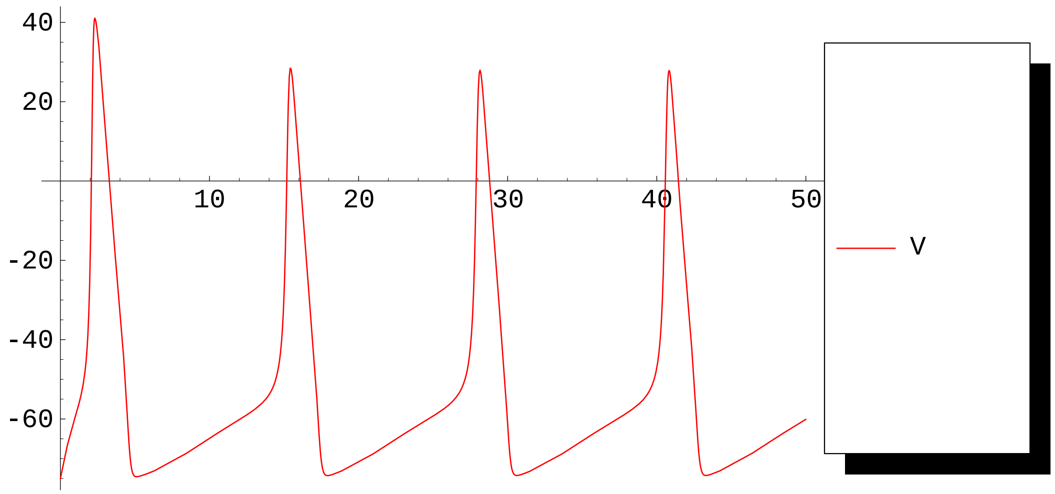
Effect of Applied Current in the Hodgkin−Huxley model

In[22]:=
```
NewModelHH = resetParameter[ModelHH, {II → 15}];
NewSolnHH = SBMLNDSolve[NewModelHH, 50];
SBMLPlot[NewSolnHH, {m, h, n}, PlotRange → All, ImageSize → {450, 200}];
VPlot3 = SBMLPlot[NewSolnHH, {V}, PlotRange → All, ImageSize → {450, 200}];
```





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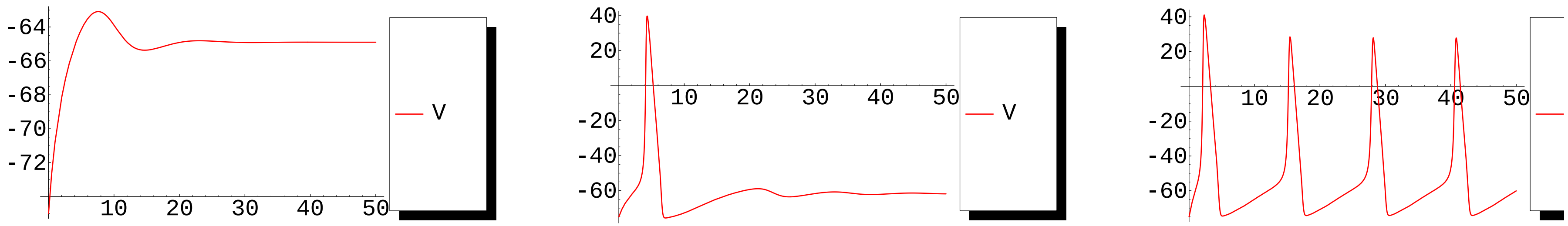
Some of the Mathematical Questions Addressed in this Course

```
In[30]:= Show[GraphicsArray[{VPlot1, VPlot2, VPlot3}], ImageSize → {250 * 3, 120}];
```



- **What solution bifurcation occurs in the transition:**
  −from a stationary state to repeated, autonomous spiking?

- **In the spikes, there are phases of slower variation inbetween phases of very rapid change**
  −Are there multiple time−scales involved?

- **What numerical methods are stable for integrating the stiff ODE:**
  −Observed oscillations are 'real' and not a numerical artifact/effect?

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Some of the Biological Modelling Questions Addressed in this Course

- **What dynamical behaviors can occur in gene systems:**
  - **−bistable/hysteretic/irreversible switches**
  - **−relaxation oscillations, bursting phenomenon, mixed−mode oscillations**

- **What are the motifs that occur frequently in biological networks?**
  - **−feed−forward**
  - **−activator−inhibitor pair**
  - **...**

- **What are the dynamical implications?**

- **How to design gene systems that exhibit switching behavior, and/or oscillations?**

2−Dimensional Reduced System: Phase Plane Analysis

In[31]:=
```
MorrisLecarODE =
  {V'[t] == -g_Ca m_∞[V[t]] (V[t] - V_Ca) -
     g_K w[t] (V[t] - V_K) - g_L (V[t] - V_L) + I_app,
   w'[t] == ϕ (w_∞[V[t]] - w[t]) / τ[V[t]] };

m_∞[V_] := 0.5 (1 + Tanh[(V - v1) / v2]);
w_∞[V_] := 0.5 (1 + Tanh[(V - v3) / v4]);
τ[V_] := 1 / Cosh[(V - v3) / (2 v4)];

MorrisLecarODE // TableForm
```

Out[35]//TableForm=

$$V'[t] == I\_app - 0.5\, g\_Ca \left(1 + \text{Tanh}\left[\frac{-v1+V[t]}{v2}\right]\right) (-V\_Ca + V[t]) - g\_L\, (-V\_L + V[t]) - g\_K\, (-V\_K + V[t])\, w[t]$$

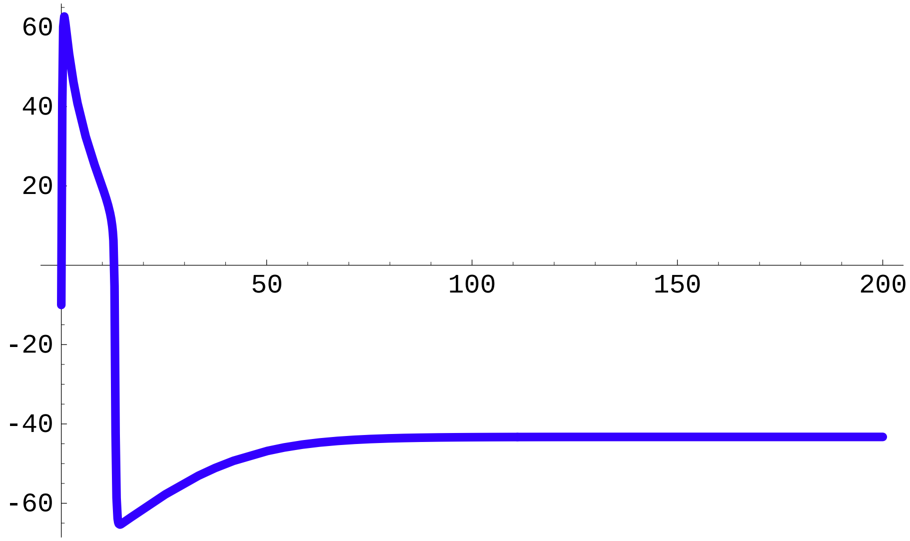
$$w'[t] == \phi\, \text{Cosh}\left[\frac{-v3+V[t]}{2\, v4}\right] \left(0.5 \left(1 + \text{Tanh}\left[\frac{-v3+V[t]}{v4}\right]\right) - w[t]\right)$$

Morris−Lecar Model: Time−Series

In[36]:=
```
MorrisLecarParamRules1 =
 {g_Ca → 4.4, v1 → -1.2, v2 → 18, v3 → 2, v4 → 30, φ → 0.04, g_K → 8,
  g_L → 2, V_L → -69, g_K → 8, V_K → -84, V_Ca → 120 , I_app → 60};
ODEIC = Join[MorrisLecarODE /. MorrisLecarParamRules1 ,
  {w[0] == 0.01, V[0] == -10}];

MorrisLecarSol1 = NDSolve[ ODEIC, {V, w} , {t, 0, 200}];

Plot[V[t] /. MorrisLecarSol1, {t, 0, 200},
 PlotStyle → {Thickness[0.01], Hue[0.7]}, ImageSize -> {400, 200}];
Null
```

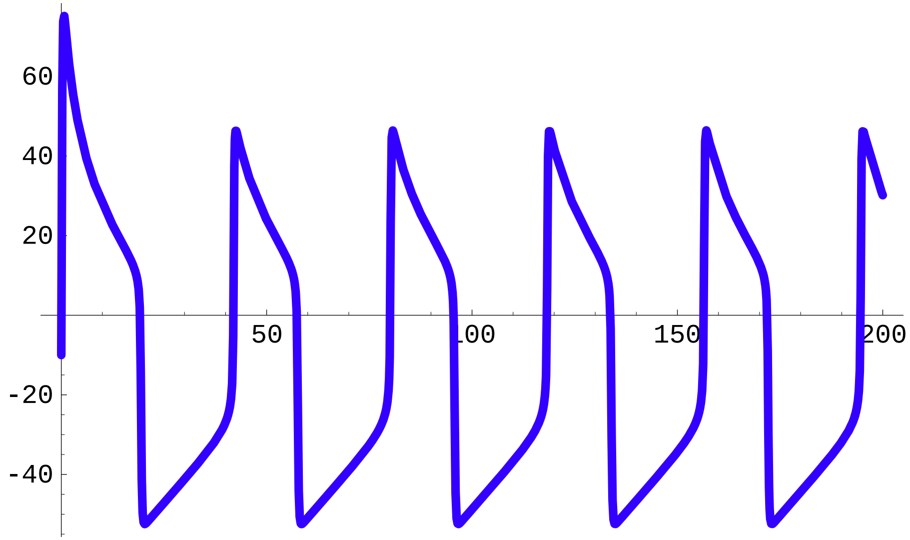


Morris−Lecar Model: Time−Series

In[50]:=
```
MorrisLecarParamRules2 =
 {g_Ca → 4.4, v1 → -1.2, v2 → 18, v3 → 2, v4 → 30, ϕ → 0.04, g_K → 8,
  g_L → 2, V_L → -69, g_K → 8, V_K → -84, V_Ca → 120 , I_app → 150};
ODEIC = Join[MorrisLecarODE /. MorrisLecarParamRules2 ,
  {w[0] == 0.01, V[0] == -10}];

MorrisLecarSol2 = NDSolve[ ODEIC, {V, w} , {t, 0, 200}];

Plot[V[t] /. MorrisLecarSol2, {t, 0, 200},
 PlotStyle → {Thickness[0.01], Hue[0.7]}, ImageSize -> {400, 200}];
```



Null Clines

In[28]:=
```
MorrisLecarNullClines = MorrisLecarODE /. {V′[t] → 0, w′[t] → 0} // TableForm
```

Out[28]//TableForm=

$0 == I\_app - 0.5\, g\_Ca\, (1 + \mathrm{Tanh}[\frac{-v1+V[t]}{v2}])\, (-V\_Ca + V[t]) - g\_L\, (-V\_L + V[t]) - g\_K\, (-V\_K + V[$

$0 == \phi\, \mathrm{Cosh}[\frac{-v3+V[t]}{2\, v4}]\, (0.5\, (1 + \mathrm{Tanh}[\frac{-v3+V[t]}{v4}]) - w[t])$

In[29]:=
```
MorrisLecarNullClines /. MorrisLecarParamRules2 // TableForm
```

Out[29]//TableForm=

$0 == 150 - 2.2\, (1 + \mathrm{Tanh}[\frac{1}{18}\, (1.2 + V[t])])\, (-120 + V[t]) - 2\, (69 + V[t]) - 8\, (84 + V[t$

$0 == 0.04\, \mathrm{Cosh}[\frac{1}{60}\, (-2 + V[t])]\, (0.5\, (1 + \mathrm{Tanh}[\frac{1}{30}\, (-2 + V[t])]) - w[t])$

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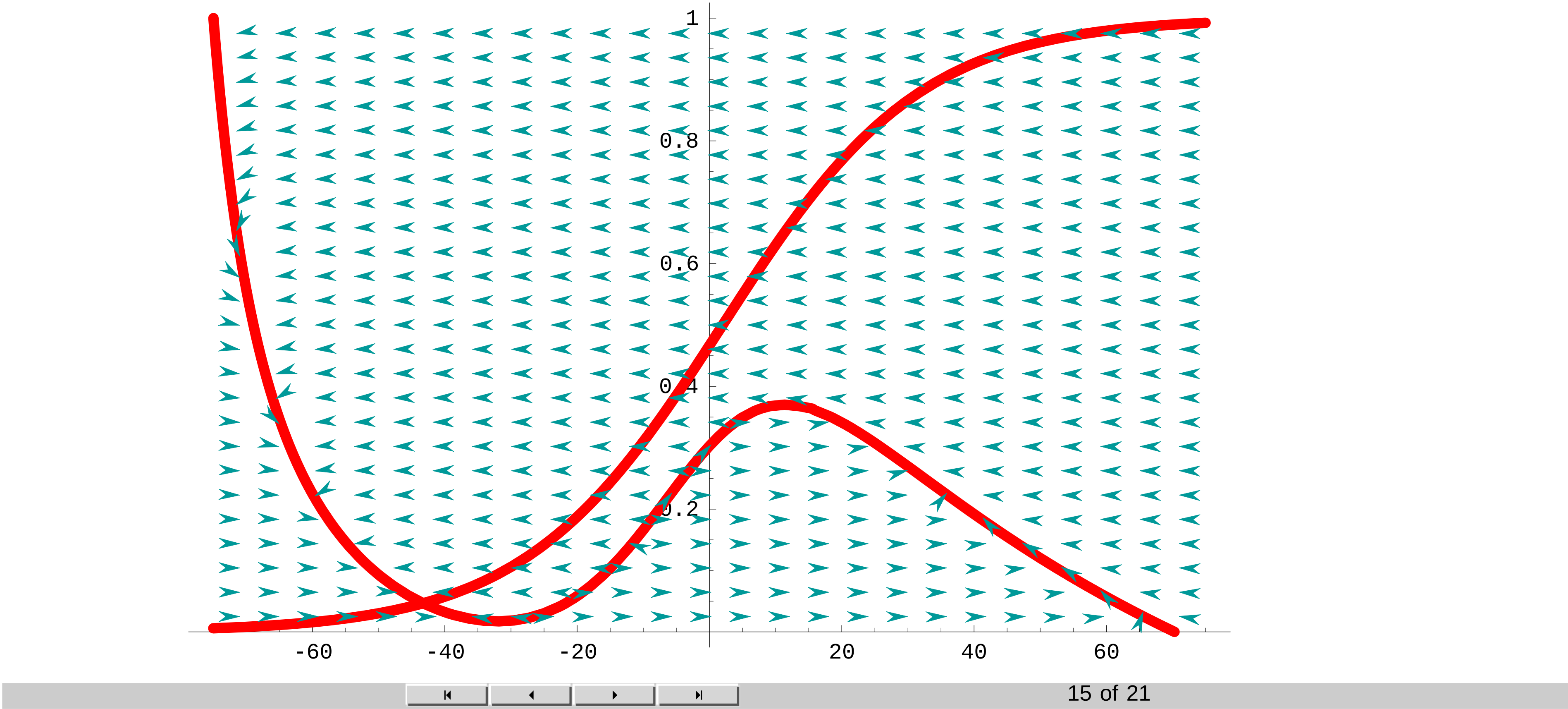
Null Clines and Phase Plane Plot: Low Applied Current

In[30]:=
```
<< DiffEqs`DEGraphics`

MorrisLecarParamRules1 = {g_Ca → 4.4, v1 → -1.2, v2 → 18, v3 → 2, v4 → 30, ϕ → 0.04,
  g_K → 8, g_L → 2, V_L → -69, g_K → 8, V_K → -84, V_Ca → 120 , I_app → 60};
VF1 = Map[ #[[2]] &, MorrisLecarODE /. MorrisLecarParamRules1] /. {V[t] -> V, w[t] -> w

PhasePlot[VF1, {t, 0, 10}, {V, -75, 75}, {w, 0, 1}, InitialPoints → None,
 ShowNullclines → True, ShowEquilibriumPoints → False, ImageSize → {600, 300},
 Gap → 0.0, Arrows → {25, 25}, PlotStyle → Thickness[0.02],
 NullclineStyle → { RGBColor[1, 0, 00], Thickness[0.01]}];
Null
```


1
0.8
0.6
0.4
0.2
-60
-40
-20
20
40
60
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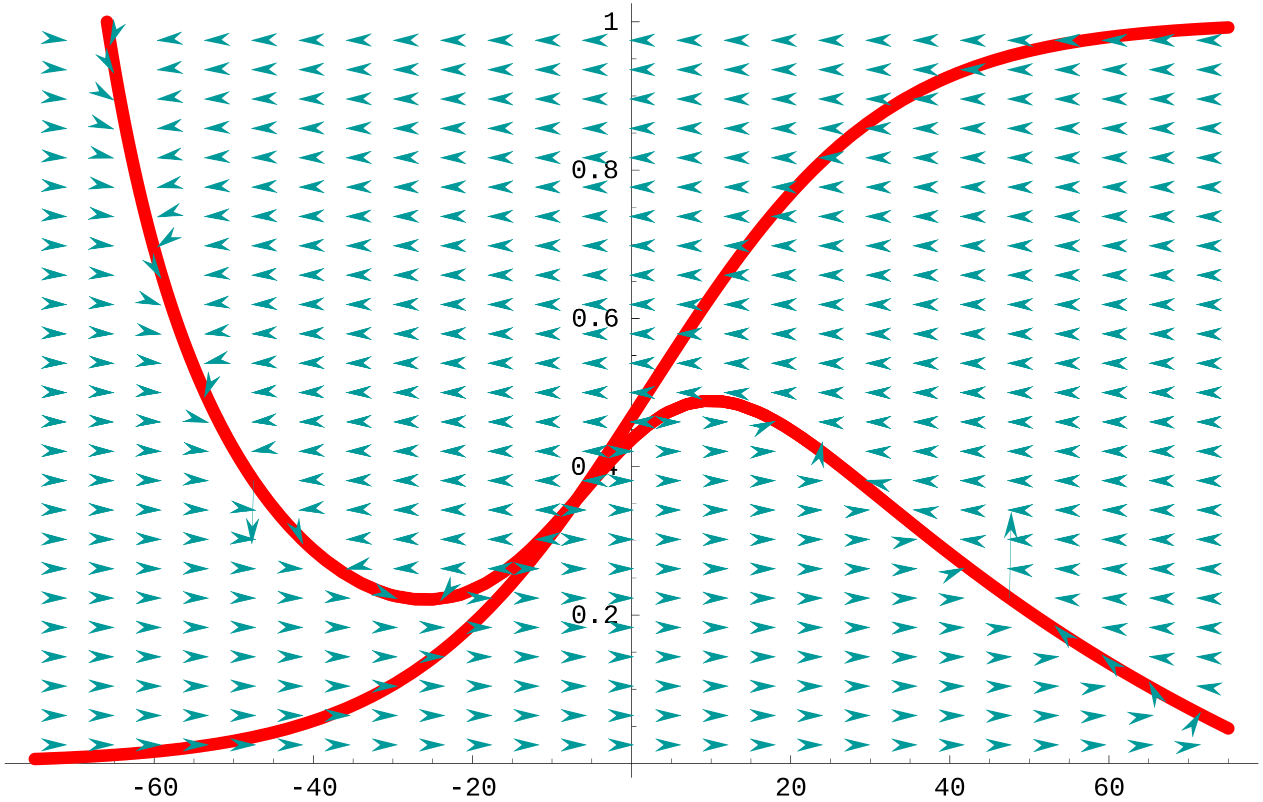
Null Clines and Phase Plane Plot: High Applied Current

In[34]:=
```
MorrisLecarParamRules2 =
 {g_Ca → 4.4, v1 → -1.2, v2 → 18, v3 → 2, v4 → 30, ϕ → 0.04, g_K → 8,
  g_L → 2, V_L → -69, g_K → 8, V_K → -84, V_Ca → 120 , I_app → 150};
VF2 = Map[ #[[2]] &, MorrisLecarODE /. MorrisLecarParamRules2] /. {V[t] -> V, w[t] -> w

PhasePlot[VF2, {t, 0, 10}, {V, -75, 75}, {w, 0, 1}, InitialPoints → None,
 ShowNullclines → True, ShowEquilibriumPoints → False, ImageSize → {600, 300},
 Gap → 0.0, Arrows → {25, 25}, PlotStyle → Thickness[0.02],
 NullclineStyle → { RGBColor[1, 0, 00], Thickness[0.01]}];
Null
```



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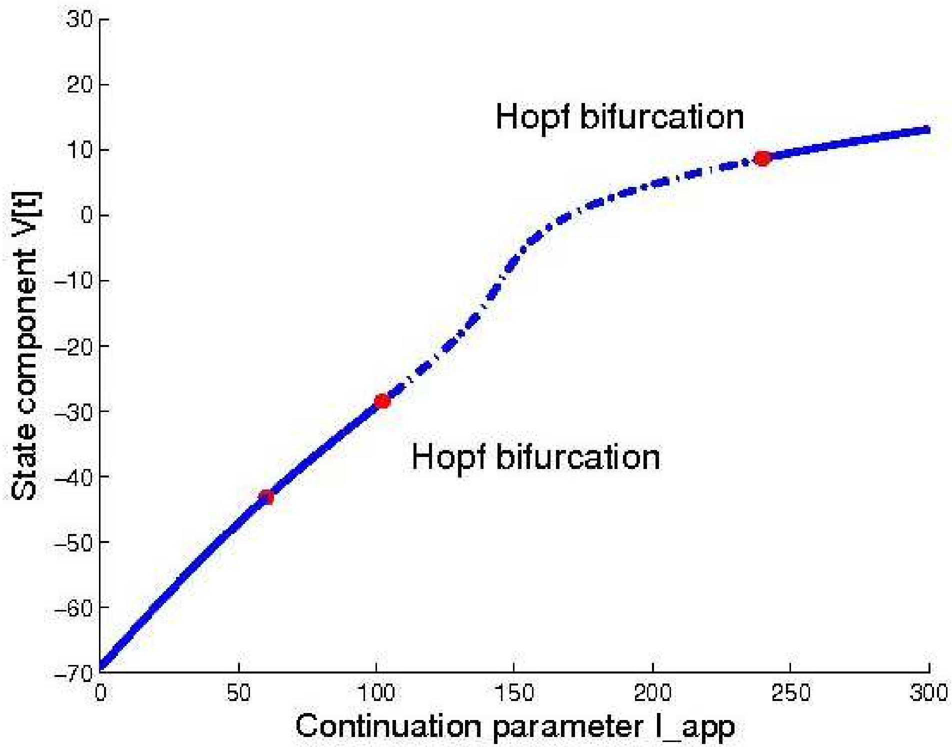
Solution Continuation and Bifurcation Detection

• The system becomes unstable as I_app is increased.

• The structural stability is lost as an eigenvalue pair crosses the imaginary axis from negative half−plane.

• To locate the value of I_app were lost−of−stability occurs, we can:
−continue the equilibrium solution with respect to I_app
−detect change in stability using test function for Hopf bifurcation.

```
In[26]:= MCBifPlot = Import["~/Teaching/NoteBooks/MATCONT_FILES/MorrisLecar_Bif.jpg"];
         Show[MCBifPlot, ImageSize → {400, 300}];
```


Hopf bifurcation
Hopf bifurcation
State component V[t]
Continuation parameter I_app
30
20
10
0
−10
−20
−30
−40
−50
−60
−70
0
50
100
150
200
250
300

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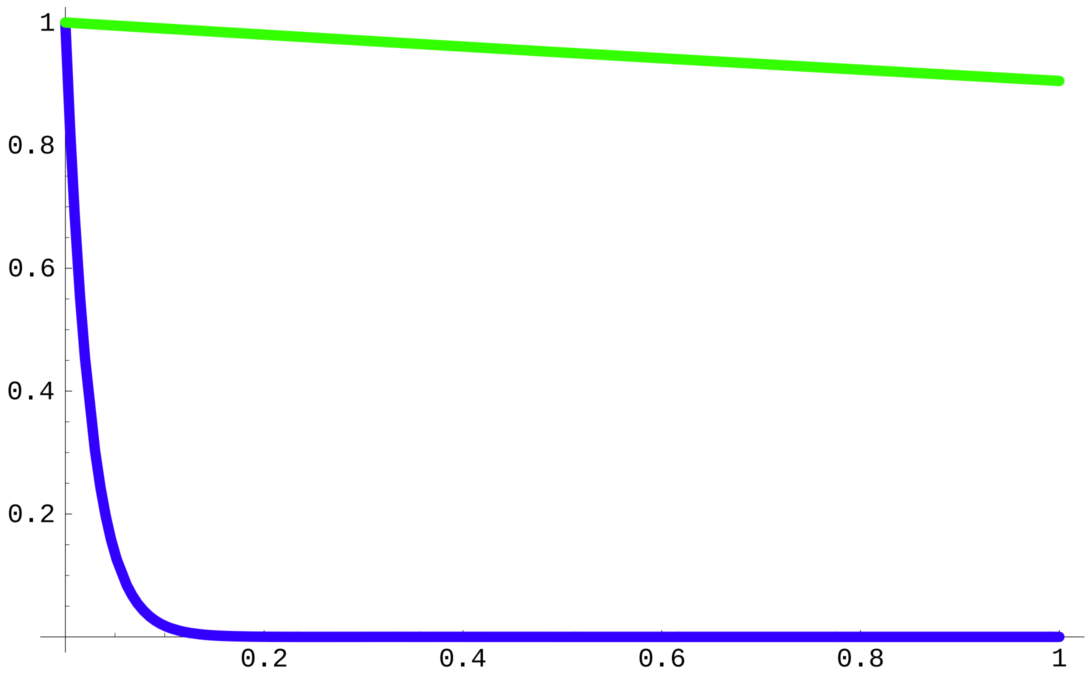
Stiff ODE System

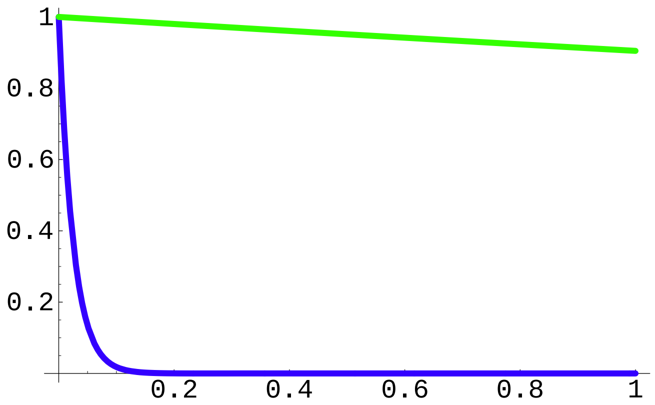
In[54]:=
```
sol = NDSolve[{y'[x] == -40 y[x], z'[x] == -1/10 z[x], y[0] == z[0] == 1},
  {y, z}, {x, 0, 1}, Method -> "BDF", StartingStepSize -> 0.1,
  PrecisionGoal -> 3, AccuracyGoal -> 3, MaxSteps -> 10^6];

Plot[Evaluate[{y[x], z[x]} /. sol], {x, 0, 1}, PlotRange -> All,
 PlotStyle -> {{Thickness[0.01], Hue[0.7]}, {Thickness[0.01], Hue[0.3]}},
 ImageSize -> {500, 250}]
Null
```



Out[55]= - Graphics -

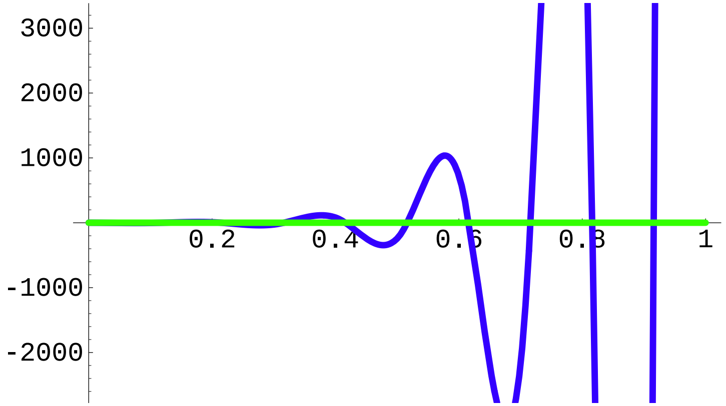
Stiff ODE System : Stability of Numerical Methods

```
In[39]:= sol = NDSolve[{y'[x] == -40 y[x], z'[x] == -1/10 z[x], y[0] == z[0] == 1}, {y, z}, {x, 0, 1},
           Method → "BDF", StartingStepSize → 0.1, PrecisionGoal → 3, AccuracyGoal → 3, MaxSteps → 10^6];
         Plot[Evaluate[{y[x], z[x]} /. sol], {x, 0, 1}, PlotRange → All,
          PlotStyle → {{Thickness[0.01], Hue[0.7]}, {Thickness[0.01], Hue[0.3]}}, ImageSize → {300, 150}]
```




```
Out[40]= - Graphics -
```

In[41]:=
```
sol = NDSolve[{y'[x] == -40 y[x], z'[x] == -1/10 z[x], y[0] == z[0] == 1}, {y, z},
   {x, 0, 1}, Method → "ExplicitEuler", StartingStepSize → 0.1, PrecisionGoal → 3, AccuracyGoal → 3];
Plot[Evaluate[{y[x], z[x]} /. sol], {x, 0, 1}, PlotStyle → {{Thickness[0.01], Hue[0.7]}, {Thickness[0.01], Hue[0.3]}},
 ImageSize → {300, 150}]
```



Out[42]= - Graphics -

Cell Cycle Model: Chen et al, 2004

```
ModelCellCycle = SBMLRead["~/Teaching/SBMLModels/Chen2004_CellCycle.xml", verbose → True];
SolnCellCycle = SBMLNDSolve[ModelCellCycle, 1000];
```

File Name:~/Teaching/SBMLModels/Chen2004_CellCycle.xml
SBML Level 2 Version 1

Model name: Chen2004_CellCycle
Model id: Model2
Model metaid: metaid_0000002

Function Definitions

Unit Definitions (Excluding Built–in Units)

ID	MetaID	Name	Formula
time	metaid_0000366	min	60*second

Compartments

ID	MetaID	Name	Dimension	Size	Units	Derived Units	Outside	Constant
cell_0	metaid_0000171	cell	3	1	volume	litre	…	True

Species

ID	Name	Compartment	initialType	Value	Units of the Species	Deriv
BCK2_1	BCK2	cell_0	…	…	substance	mole
BUB2_2	BUB2	cell_0	initialAmount	0.2	substance	mole
BUD_3	BUD	cell_0	initialAmount	0.008473	substance	mole
C2_4	C2	cell_0	initialAmount	0.238404	substance	mole
C2P_5	C2P	cell_0	initialAmount	0.024034	substance	mole
C5_6	C5	cell_0	initialAmount	0.070081	substance	mole
C5P_7	C5P	cell_0	initialAmount	0.006878	substance	mole
CDC14_8	CDC14	cell_0	initialAmount	0.468344	substance	mole
CDC14T_9	CDC14T	cell_0	initialAmount	2	substance	mole
CDC15_10	CDC15	cell_0	initialAmount	0.656533	substance	mole
CDC15i_11	CDC15i	cell_0	initialAmount	0.343466	substance	mole
CDC20_12	CDC20	cell_0	initialAmount	0.444296	substance	mole
CDC20i_13	CDC20i	cell_0	initialAmount	1.472044	substance	mole
CDC6_14	CDC6	cell_0	initialAmount	0.10758	substance	mole
CDC6P_15	CDC6P	cell_0	initialAmount	0.015486	substance	mole
CDC6T_16	CDC6T	cell_0	…	…	substance	mole
CDH1_17	CDH1	cell_0	initialAmount	0.930499	substance	mole
CDH1i_18	CDH1i	cell_0	initialAmount	0.0695	substance	mole

CKIT␣19	CKIT	cell␣0	⋯	⋯	substance	mole
CLB2␣20	CLB2	cell␣0	initialAmount	0.1469227	substance	mole
CLB2T␣21	CLB2T	cell␣0	initialAmount	0.17	substance	mole
CLB5␣22	CLB5	cell␣0	initialAmount	0.0518014	substance	mole
CLB5T␣23	CLB5T	cell␣0	initialAmount	0.12	substance	mole
CLN2␣24	CLN2	cell␣0	initialAmount	0.0652511	substance	mole
CLN3␣25	CLN3	cell␣0	⋯	⋯	substance	mole
ESP1␣27	ESP1	cell␣0	initialAmount	0.301313	substance	mole
F2␣29	F2	cell␣0	initialAmount	0.236058	substance	mole
F2P␣30	F2P	cell␣0	initialAmount	0.0273938	substance	mole
F5␣31	F5	cell␣0	initialAmount	0.0000724000000000001	substance	mole
F5P␣32	F5P	cell␣0	initialAmount	0.0000791000000000001	substance	mole
IE␣33	IE	cell␣0	initialAmount	0.8985	substance	mole
IEP␣34	IEP	cell␣0	initialAmount	0.1015	substance	mole
LTE1␣35	LTE1	cell␣0	initialAmount	0.1	substance	mole
MAD2␣36	MAD2	cell␣0	initialAmount	0.01	substance	mole
MASS␣37	MASS	cell␣0	initialAmount	1.206019	substance	mole
MCM1␣38	MCM1	cell␣0	⋯	⋯	substance	mole
NET1␣40	NET1	cell␣0	initialAmount	0.018645	substance	mole
NET1P␣41	NET1P	cell␣0	initialAmount	0.970271	substance	mole
NET1T␣42	NET1T	cell␣0	initialAmount	2.8	substance	mole
ORI␣43	ORI	cell␣0	initialAmount	0.000909	substance	mole
PDS1␣44	PDS1	cell␣0	initialAmount	0.025612	substance	mole
PE␣45	PE	cell␣0	initialAmount	0.7	substance	mole
PPX␣46	PPX	cell␣0	initialAmount	0.123179	substance	mole
RENT␣47	RENT	cell␣0	initialAmount	1.04954	substance	mole
RENTP␣48	RENTP	cell␣0	initialAmount	0.6	substance	mole
SBF␣49	SBF	cell␣0	⋯	⋯	substance	mole
SIC1␣50	SIC1	cell␣0	initialAmount	0.0228776	substance	mole
SIC1P␣51	SIC1P	cell␣0	initialAmount	0.00641	substance	mole
SIC1T␣52	SIC1T	cell␣0	⋯	⋯	substance	mole
SPN␣53	SPN	cell␣0	initialAmount	0.03	substance	mole
SWI5␣54	SWI5	cell␣0	initialAmount	0.95	substance	mole
SWI5P␣55	SWI5P	cell␣0	initialAmount	0.02	substance	mole
TEM1GDP␣56	TEM1GDP	cell␣0	initialAmount	0.1	substance	mole
TEM1GTP␣57	TEM1GTP	cell␣0	initialAmount	0.9	substance	mole

Global Parameters

Rules

Reactions, contexts suppressed

ID	MetaID	Name	Fast	Reaction
Growth_225	metaid_0000262	Growth	False	∅ → MASS_37
SynthesisofCLN_226	metaid_0000263	Synthesis of CLN2	False	∅ → CLN2_24
DegradationofCLN_227	metaid_0000264	Degradation of CLN2	False	CLN2_24 → ∅
SynthesisofCLB_228	metaid_0000265	Synthesis of CLB2	False	∅ → CLB2_20
DegradationofCLB_229	metaid_0000266	Degradation of CLB2	False	CLB2_20 → ∅
SynthesisofCLB_230	metaid_0000267	Synthesis of CLB5	False	∅ → CLB5_22
DegradationofCLB_231	metaid_0000268	Degradation of CLB5	False	CLB5_22 → ∅
SynthesisofSIC_232	metaid_0000269	Synthesis of SIC1	False	∅ → SIC1_50
PhosphorylationofSIC_233	metaid_0000270	Phosphorylation of SIC1	False	SIC1_50 → SIC1P_51
DephosphorylationofSIC_234	metaid_0000271	Dephosphorylation of SIC1	False	SIC1P_51 → SIC1_50
FastDegradationofSICP_235	metaid_0000272	Fast Degradation of SIC1P	False	SIC1P_51 → ∅
AssocofCLBandSIC_236	metaid_0000273	Assoc. of CLB2 and SIC1	False	CLB2_20 + SIC1_50 → C2
DissocofCLBSICcomplex_237	metaid_0000274	Dissoc. of CLB2/SIC1 complex	False	C2_4 → CLB2_20 + SIC1_
AssocofCLBandSIC_238	metaid_0000275	Assoc. of CLB5 and SIC1	False	CLB5_22 + SIC1_50 → C5
DissocofCLBSIC_239	metaid_0000276	Dissoc. of CLB5/SIC1	False	C5_6 → CLB5_22 + SIC1_
PhosphorylationofC_240	metaid_0000277	Phosphorylation of C2	False	C2_4 → C2P_5
DephosphorylationofCP_241	metaid_0000278	Dephosphorylation of C2P	False	C2P_5 → C2_4
_242	metaid_0000279	Phosphorylation of C5	False	C5_6 → C5P_7
_243	metaid_0000280	Dephosphorylation of C5P	False	C5P_7 → C5_6
DegradationofCLBinC_244	metaid_0000281	Degradation of CLB2 in C2	False	C2_4 → SIC1_50
_245	metaid_0000282	Degradation of CLB5 in C5	False	C5_6 → SIC1_50
DegradationofSICinCP_246	metaid_0000283	Degradation of SIC1 in C2P	False	C2P_5 → CLB2_20
_247	metaid_0000284	Degradation of SIC1P in C5P	False	C5P_7 → CLB5_22
DegradationofCLBinCP_248	metaid_0000285	Degradation of CLB2 in C2P	False	C2P_5 → SIC1P_51

_249	metaid_0000286	Degradation of CLB5 in C5P	False	C5P_7 → SIC1P_51
CDCanotherCKIlikeSIC_250	metaid_0000287	CDC6 synthesis	False	∅ → CDC6_14
_251	metaid_0000288	Phosphorylation of CDC6	False	CDC6_14 → CDC6P_15
_252	metaid_0000289	Dephosphorylation of CDC6	False	CDC6P_15 → CDC6_14
_253	metaid_0000290	Degradation of CDC6P	False	CDC6P_15 → ∅
_254	metaid_0000291	CLB2/CDC6 complex formation	False	CDC6_14 + CLB2_20 → F2
_255	metaid_0000292	CLB2/CDC6 dissociation	False	F2_29 → CDC6_14 + CLB2
_256	metaid_0000293	CLB5/CDC6 complex formation	False	CDC6_14 + CLB5_22 → F5
_257	metaid_0000294	CLB5/CDC6 dissociation	False	F5_31 → CDC6_14 + CLB5
_258	metaid_0000295	F2 phosphorylation	False	F2_29 → F2P_30
_259	metaid_0000296	F2P dephosphorylation	False	F2P_30 → F2_29
_260	metaid_0000297	F5 phosphorylation	False	F5_31 → F5P_32
_261	metaid_0000298	F5P dephosphorylation	False	F5P_32 → F5_31
_262	metaid_0000299	CLB2 degradation in F2	False	F2_29 → CDC6_14
_263	metaid_0000300	CLB5 degradation in F5	False	F5_31 → CDC6_14
_264	metaid_0000301	CDC6 degradation in F2P	False	F2P_30 → CLB2_20
_265	metaid_0000302	CDC6 degradation in F5P	False	F5P_32 → CLB5_22
_266	metaid_0000303	CLB2 degradation in F2P	False	F2P_30 → CDC6P_15
_267	metaid_0000304	CLB5 degradation in F5P	False	F5P_32 → CDC6P_15
SynthesisofSWI_268	metaid_0000305	Synthesis of SWI5	False	∅ → SWI5_54
DegradationofSWI_269	metaid_0000306	Degradation of SWI5	False	SWI5_54 → ∅
DegradationofSWIP_270	metaid_0000307	Degradation of SWI5P	False	SWI5P_55 → ∅
ActivationofSWI_271	metaid_0000308	Activation of SWI5	False	SWI5P_55 → SWI5_54
InactivationofSWI_272	metaid_0000309	Inactivation of SWI5	False	SWI5_54 → SWI5P_55
ActivationofIEP_273	metaid_0000310	Activation of IEP	False	IE_33 → IEP_34
Inactivation_274_IEP	metaid_0000311	Inactivation	False	IEP_34 → IE_33
SynthesisofinactiveCDC_275	metaid_0000312	Synthesis of inactive CDC20	False	∅ → CDC20i_13
DegradationofinactiveCDC_276	metaid_0000313	Degradation of inactiveCDC20	False	CDC20i_13 → ∅
DegradationofactiveCDC_277	metaid_0000314	Degradation of active CDC20	False	CDC20_12 → ∅
ActivationofCDC_278	metaid_0000315	Activation of CDC20	False	CDC20i_13 → CDC20_12
Inactivation_274_CDC20	metaid_0000316	Inactivation	False	CDC20_12 → CDC20i_13
_279	metaid_0000317	CDH1 synthesis	False	∅ → CDH1_17
_280	metaid_0000318	CDH1 degradation	False	CDH1_17 → ∅
_281	metaid_0000319	CDH1i degradation	False	CDH1i_18 → ∅
Activation_282	metaid_0000320	CDH1i activation	False	CDH1i_18 → CDH1_17

Inactivation_274_CDH1	metaid_0000321	Inactivation	False	CDH1_17 → CDH1i_18
_283	metaid_0000322	CDC14 synthesis	False	∅ → CDC14_8
_284	metaid_0000323	CDC14 degradation	False	CDC14_8 → ∅
AssocwithNETtoformRENT_285	metaid_0000324	Assoc. with NET1 to form RENT	False	CDC14_8 + NET1_40 → RE
DissocfromRENT_286	metaid_0000325	Dissoc. from RENT	False	RENT_47 → CDC14_8 + NE
AssocwithNETPtoformRENTP_287	metaid_0000326	Assoc with NET1P to form RENTP	False	CDC14_8 + NET1P_41 → R
DissocfromRENP_288	metaid_0000327	Dissoc. from RENP	False	RENTP_48 → CDC14_8 + N
_289	metaid_0000328	Net1 synthesis	False	∅ → NET1_40
_290	metaid_0000329	Net1 degradation	False	NET1_40 → ∅
_291	metaid_0000330	Net1P degradation	False	NET1P_41 → ∅
NETphosphorylation_292	metaid_0000331	NET1 phosphorylation	False	NET1_40 → NET1P_41
dephosphorylation_293_NET1P	metaid_0000332	dephosphorylation	False	NET1P_41 → NET1_40
RENTphosphorylation_294	metaid_0000333	RENT phosphorylation	False	RENT_47 → RENTP_48
dephosphorylation_293_RENTP	metaid_0000334	dephosphorylation	False	RENTP_48 → RENT_47
DegradationofNETinRENT_295	metaid_0000335	Degradation of NET1 in RENT	False	RENT_47 → CDC14_8
DegradationofNETPinRENTP_296	metaid_0000336	Degradation of NET1P in RENTP	False	RENTP_48 → CDC14_8
DegradationofCDCinRENT_297	metaid_0000337	Degradation of CDC14 in RENT	False	RENT_47 → NET1_40
DegradationofCDCinRENTP_298	metaid_0000338	Degradation of CDC14 in RENTP	False	RENTP_48 → NET1P_41
TEMactivation_299	metaid_0000339	TEM1 activation	False	TEM1GDP_56 → TEM1GTP_5
inactivation_300_TEM1GTP	metaid_0000340	inactivation	False	TEM1GTP_57 → TEM1GDP_5
CDCactivation_301	metaid_0000341	CDC15 activation	False	CDC15i_11 → CDC15_10
inactivation_300_CDC15	metaid_0000342	inactivation	False	CDC15_10 → CDC15i_11
PPXsynthesis_302	metaid_0000343	PPX synthesis	False	∅ → PPX_46
degradation_303_PPX	metaid_0000344	degradation	False	PPX_46 → ∅
PDSsynthesis_304	metaid_0000345	PDS1 synthesis	False	∅ → PDS1_44
degradation_303_PDS1	metaid_0000346	degradation	False	PDS1_44 → ∅
DegradationofPDSinPE_305	metaid_0000347	Degradation of PDS1 in PE	False	PE_45 → ESP1_27
AssocwithESPtoformPE_306	metaid_0000348	Assoc. with ESP1 to form PE	False	ESP1_27 + PDS1_44 → PE
DissofromPE_307	metaid_0000349	Disso. from PE	False	PE_45 → ESP1_27 + PDS1
_308	metaid_0000350	DNA synthesis	False	∅ → ORI_43
_309	metaid_0000351	Negative regulation of DNA synthesis	False	ORI_43 → ∅

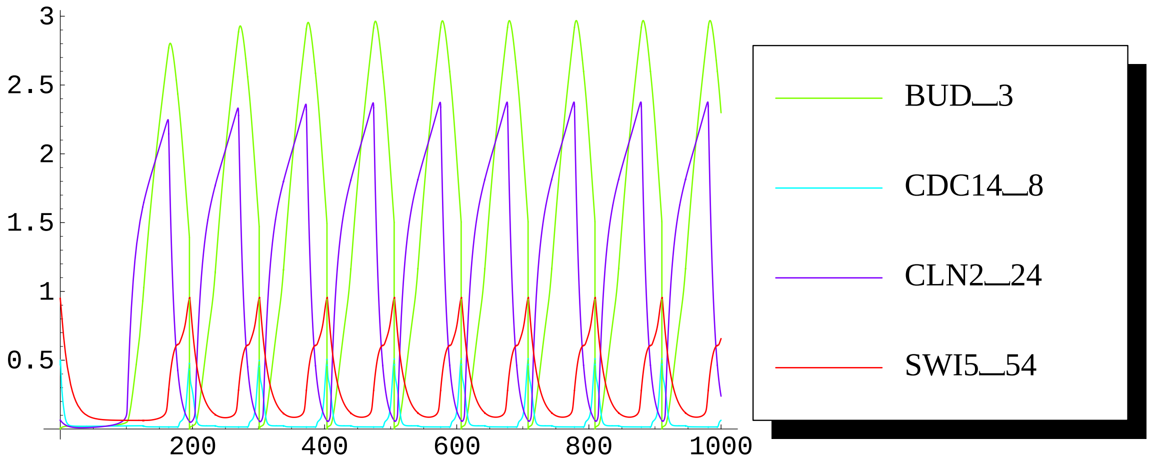
␣310	metaid␣0000352	Budding	False	∅ → BUD␣3
␣311	metaid␣0000353	Negative regulation of Cell budding	False	BUD␣3 → ∅
␣312	metaid␣0000354	Spindle formation	False	∅ → SPN␣53
␣313	metaid␣0000355	Spindle disassembly	False	SPN␣53 → ∅

Differential Equations, contexts suppressed

Events

ID	MetaID	Name	Trigger	Delay	TimeUnits	Event Assignm
event␣1	metaid␣0000359	…	CLB2␣20[t] + CLB5␣22[t] − KEZ2␣172[t] < 0	0	time	ORI␣43[t
event␣2	metaid␣0000360	…	−1 + ORI␣43[t] > 0	0	time	MAD2␣36 BUB2␣2[t
event␣3	metaid␣0000361	…	−1 + SPN␣53[t] > 0	0	time	MAD2␣36 LTE1␣35 BUB2␣2[t
event␣4	metaid␣0000362	…	CLB2␣20[t] − KEZ␣171[t] < 0	0	time	MASS␣37 LTE1␣35 BUD␣3[t] SPN␣53[t

```
In[23]:= SBMLPlot[SolnCellCycle, {CDC14_8, BUD_3, SWI5_54, CLN2_24}, ImageSize → {450, 220}];
```



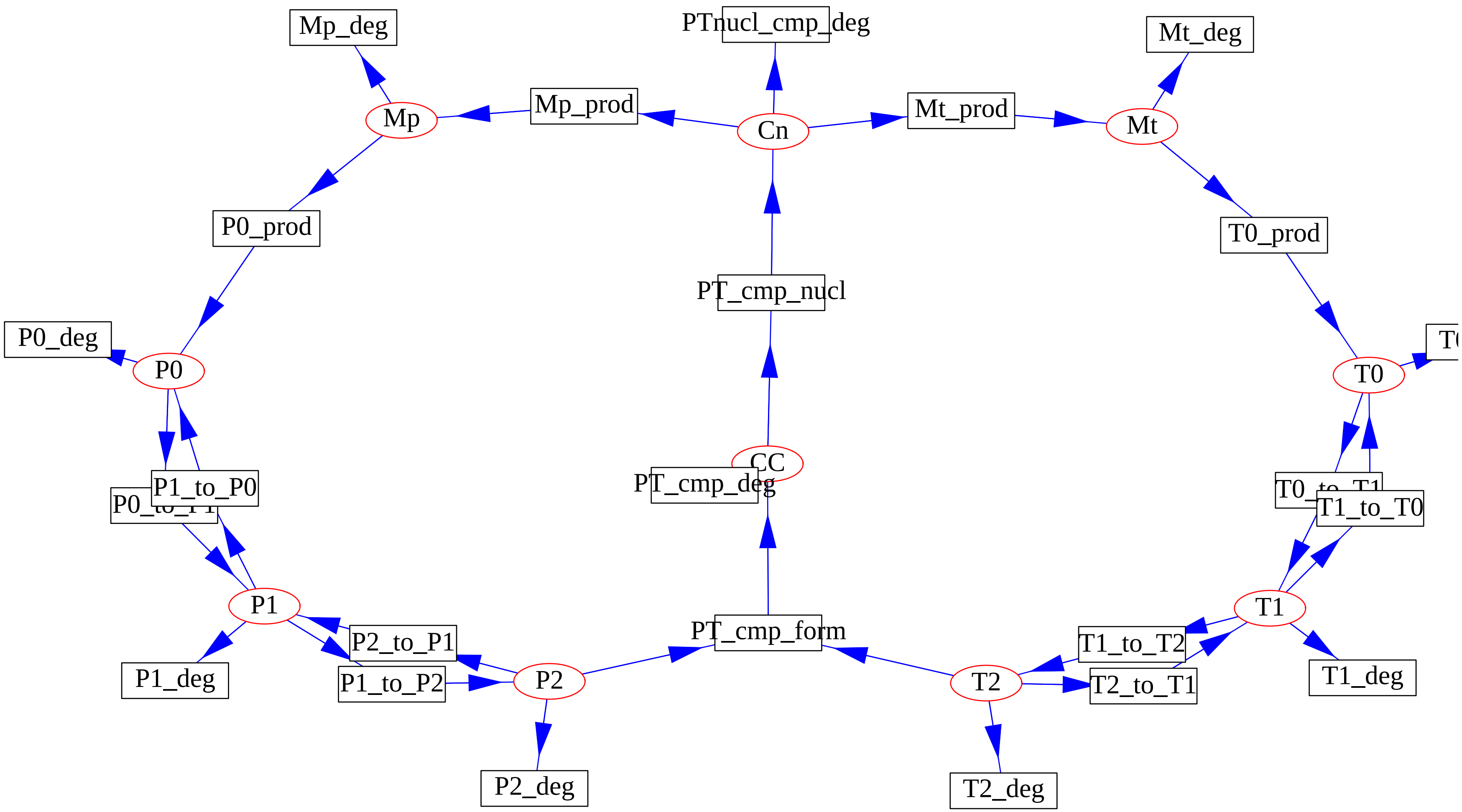
Circadian Clock Example: Leloup and Goldbeter, 1999

- **Circadian (*approximately daily*) clocks underly 24 hour sleep−wake cycle in many organisms**

- **Leloup and Goldbeter model: interlocked negative and positive regulation of *Period*, *Timeless* genes**

```
In[66]:= visualizeSBMLModel["~/Teaching/SBMLModels/CircClock_LG99.xml"];
```

CR


Mp_deg
PTnucl_cmp_deg
Mt_deg
Mp
Mp_prod
Cn
Mt_prod
Mt
P0_prod
T0_prod
PT_cmp_nucl
P0_deg
P0
T0
T(
CC
PT_cmp_deg
P1_to_P0
P0_to_P1
T0_to_T1
T1_to_T0
P1
T1
P2_to_P1
PT_cmp_form
T1_to_T2
P1_to_P2
P2
T2
T2_to_T1
P1_deg
T1_deg
P2_deg
T2_deg

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Circadian Clock Example: Leloup and Goldbeter, 1999

• Dynamical property: robust, temperature−compensated ~24 hr oscillation period

```
In[61]:= ModelCircClock = SBMLRead["~/Teaching/SBMLModels/CircClock_LG99.xml", verbose → False];
         SolnCircClock = SBMLNDSolve[ModelCircClock, 150];

In[67]:= SBMLPlot[SolnCircClock, {CC, Cn}, PlotRange → {{40, 150}, {0, 2.2}}, ImageSize → {600, 300}];
```