Circadian Clock

The circadian clock controls the daily physiological behavior of many organisms. It is known that for mammals the circadian clock resides in the hypothalamus region of the brain, and involves the synchronization of a gene regulatory network. A simple model of this network was proposed by Tyson and coworkers in 1999 and described in some detail in the SEMD textbook.

Contents

Citations

1. Tyson, J. J., C. I. Hong, C. D. Thron, B. Novak. 1999. A Simple Model of Circadian Rhythms Based on Dimerization and Proteolysis of PER and TIM. Biophysical J. 77:2411-2417.

2. SEMD Section 24.2.1.

Parameters

```
vm = 1;
km = 0.1;
vp = 0.5;
kp1 = 10;
kp2 = 0.03;
kp3 = 0.1;
Keq = 200;
Pcrit = 0.1;
Jp = 0.05;
```

Dependence of mRNA transcription rate on protein concentration

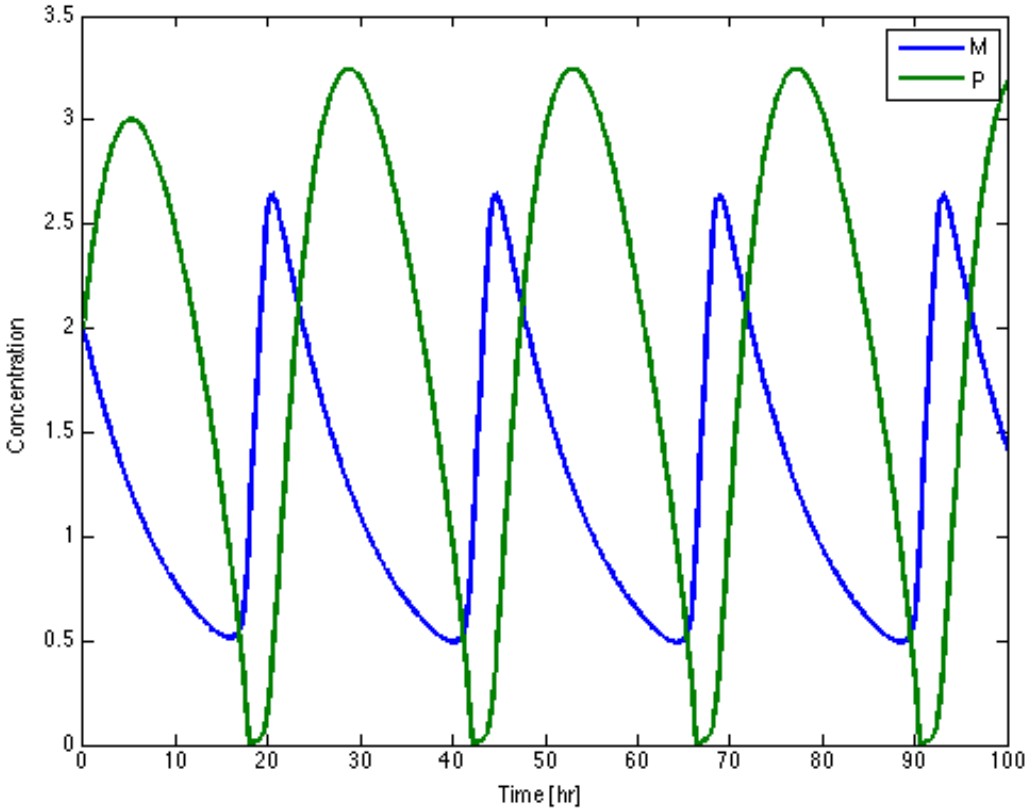
```
q = @(P) 2./(1+sqrt(1+8*Keq*P));
```

Concentration dynamics of mRNA (M) and protein (P).

```
Mdot = @(M,P) vm/(1 + (P*(1-q(P))/2/Pcrit)^2) - km*M;
Pdot = @(M,P) vp*M - (kp1*P*q(P)+kp2*P)/(Jp+P) - kp3*P;

M0 = 2;
P0 = 2;
```

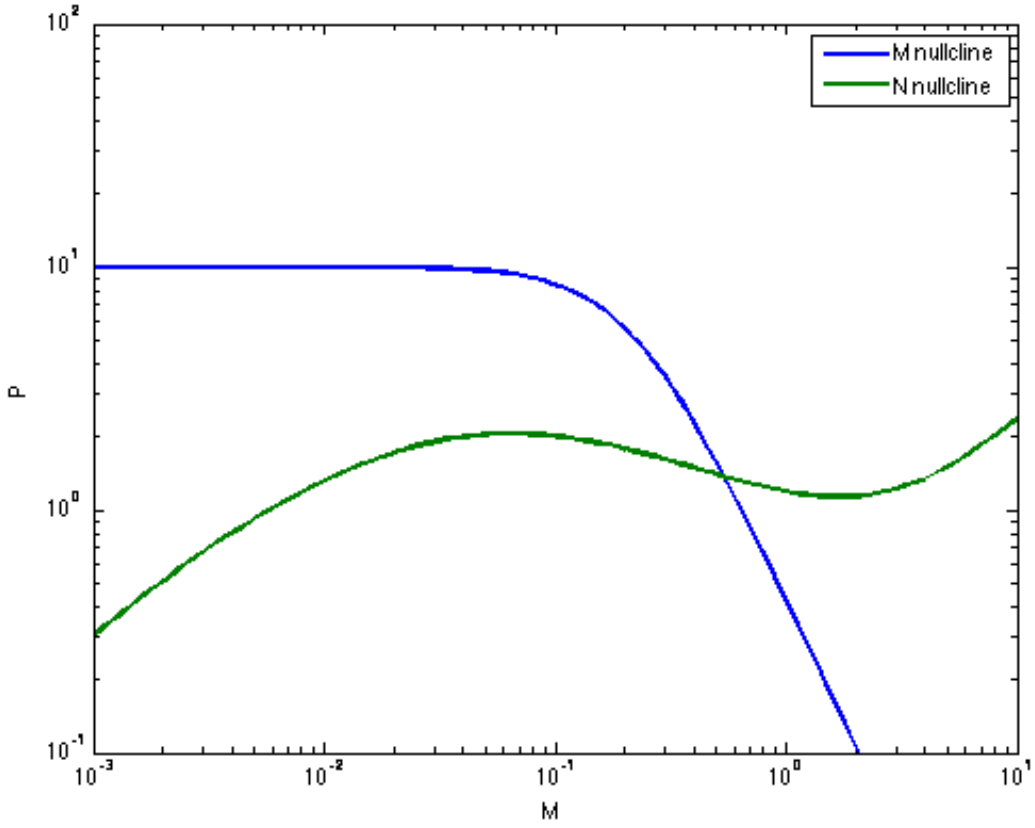
Numerical Solution

```
% Differential equations and initial conditions

deriv = @(t,x) [ ...
    Mdot(x(1),x(2));
    Pdot(x(1),x(2))];

x0 = [M0;P0];

% Calculate solution

tf = 100;
soln = ode45(@(t,x)deriv(t,x),[0 tf],x0);

% Evaluate solution

t = 0:0.1:tf;
M = deval(soln,t,1);
P = deval(soln,t,2);

% Display solution

figure(1);clf;
plot(t,M,t,P,'LineWidth',2);
xlabel('Time [hr]');
ylabel('Concentration');
legend('M','P');
```



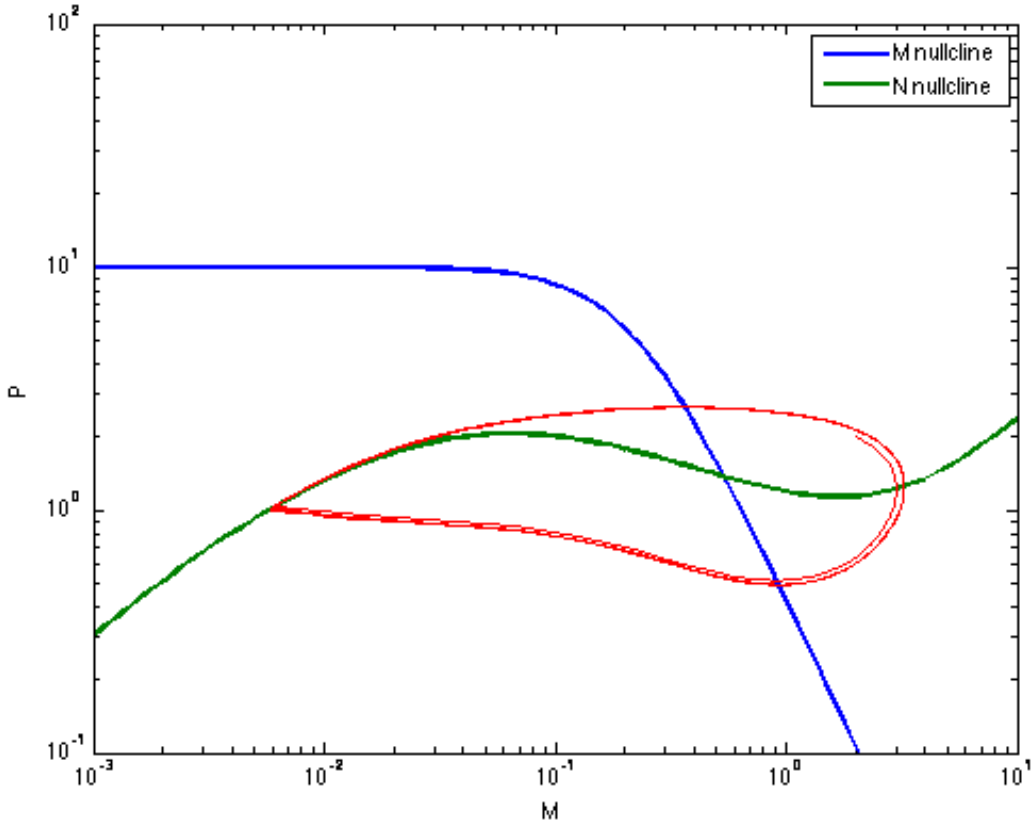
Nullclines and the Phase Plane

```
figure(2);clf;

Mnull = @(P) vm./km./(1 + (P.*(1-q(P))/2/Pcrit).^2);
Pnull = @(P) (kp1*P.*q(P)+kp2*P)./(vp*(Jp+P)) + kp3*P/vp;

Ps = logspace(-3,1,100);
loglog(Ps,Mnull(Ps),Ps,Pnull(Ps),'LineWidth',2);
axis([0.001 10 0.1 100]);
xlabel('M');
ylabel('P');
legend('M nullcline','N nullcline');
```



Plotting the solution in the phase plane demonstrates the relationship between the nullclines and solution obtained above.

```
hold on
loglog(P,M,'r');
hold off
```

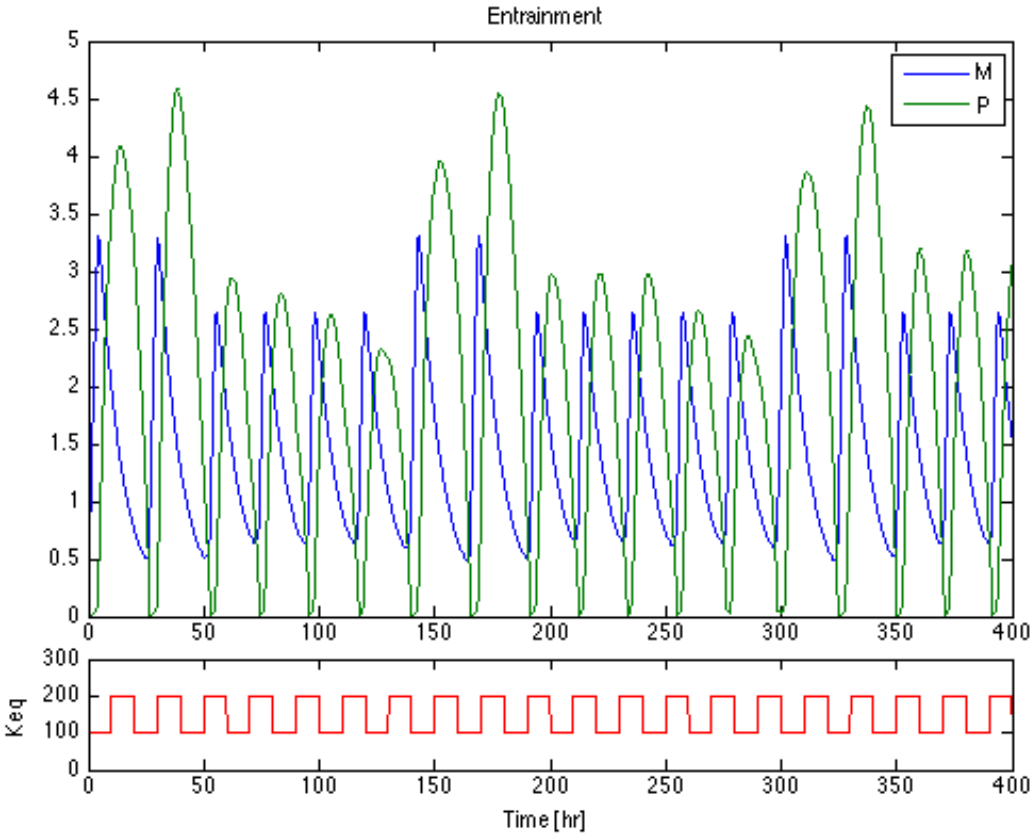


Entrainment

The circadian clock synchronizes to periodic changes in the equilbrium constant Keq. To study this phenomena, we introduce a periodic forcing function Keq(t).

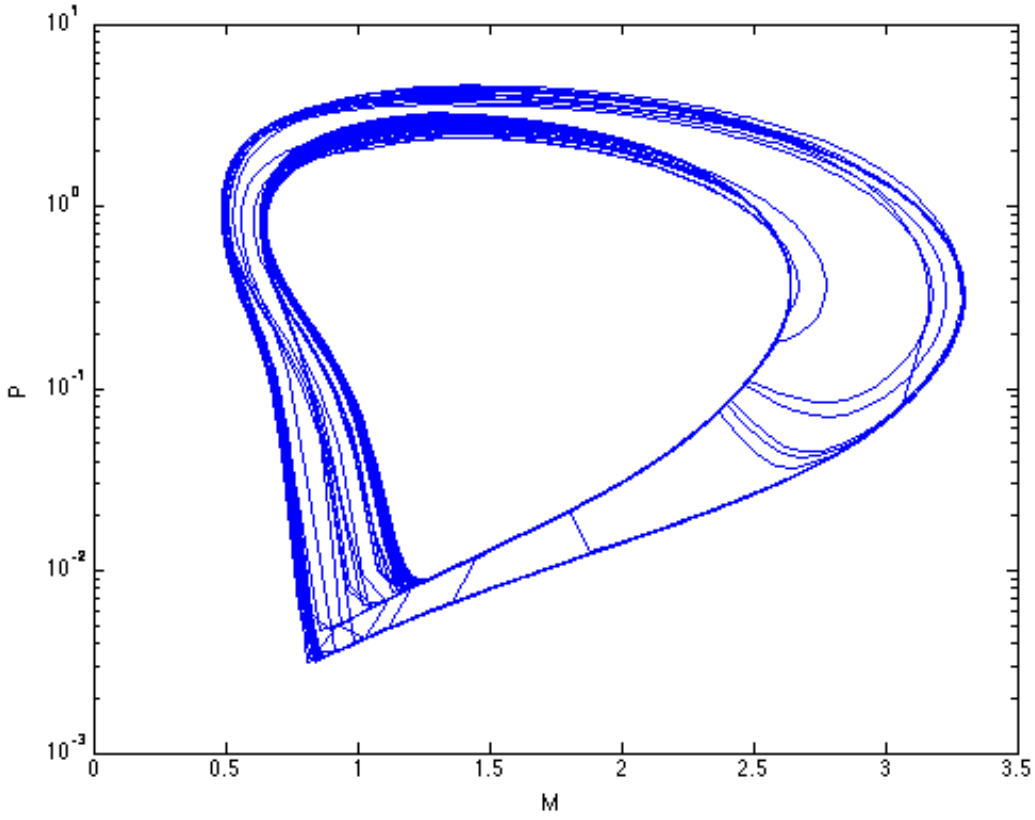
```
% The following function produces periodic square wave with period T

u = @(t,T) (mod(t,T)/T >= 0.5);

T = 20;
Keq = @(t) 100 + 100*u(t,T);

% Dependence of mRNA transcription rate on protein concentration

q = @(P,Keq) 2./(1+sqrt(1+8*Keq*P));

% Concentration dynamics of mRNA (M) and protein (P).

Mdot = @(M,P,Keq) vm/(1 + (P*(1-q(P,Keq))/2/Pcrit)^2) - km*M;
Pdot = @(M,P,Keq) vp*M - (kp1*P*q(P,Keq)+kp2*P)/(Jp+P) - kp3*P;

M0 = 0;
P0 = 0;

% Differential equations

deriv = @(t,x) [ ...
    Mdot(x(1),x(2),Keq(t));
```

```
    Pdot(x(1),x(2),Keq(t))];

x0 = [M0;P0];

% Calculate solution

tf = 400;
soln = ode45(@(t,x)deriv(t,x),[0 tf],x0);

% Evaluate and Display solution

figure(3);clf;

t = 0:0.1:tf;
subplot(5,1,[1:4])
plot(t,deval(soln,t));
legend('M','P');
title('Entrainment');

subplot(5,1,5)
plot(t,Keq(t),'r');
axis([0 tf 0 300]);
xlabel('Time [hr]');
ylabel('Keq');
```



Entrainment appears to be aperiodic

```
tf = 2000;
soln = ode45(@(t,x)deriv(t,x),[0 tf],x0,odeset('RelTol',1e-6));

% Evaluate solution

t = 400:0.1:tf;
M = deval(soln,t,1);
P = deval(soln,t,2);

figure(4);clf;

semilogy(M,P);
xlabel('M');
ylabel('P');
```



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