Atomoxetine Effect on NaV1.5

10/2018

Michael Fauler

Institute of General Physiology

Ulm University

Germany

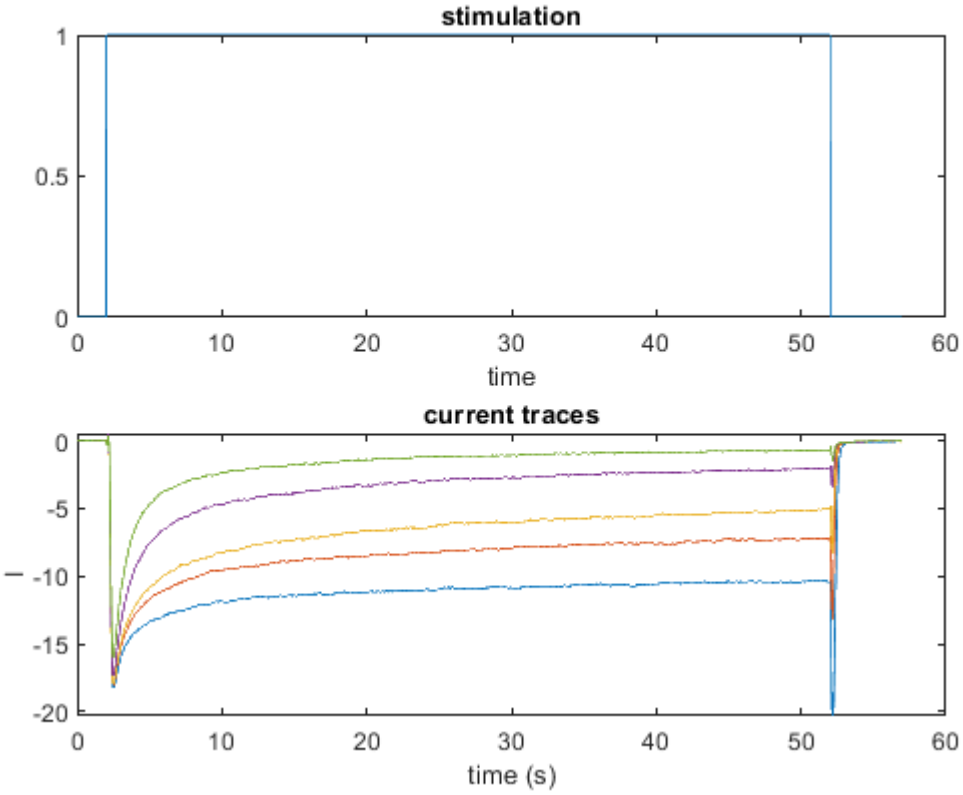
michael.fauler@uni-ulm.de

Table of Contents

Load and Prepare Data 1
Fit Exponential Decay Models to Data 4
Concentration-Response Relations 6
Local Function Definitions 8

Load and Prepare Data

```
load('Data_E53.mat'); % load data
time = DataE53S1{:,1}/1e6; %microsec->s
c_ATO(1) = 1e-3; %replace 0 by small value :-(
figure;
subplot(2,1,1);
plot(time,stim_E53(:,2));
title('stimulation');
xlabel('time');
subplot(2,1,2);
plot(time,DataE53S1{:,2:6});
title('current traces');
xlabel('time (s)');
ylabel('I');
```



Determine start and end time of stimulation protocol

```
istim1 = find(stim_E53(:,2)==1,1,'first');
istim2 = find(stim_E53(:,2)==1,1,'last');
fprintf('stimulus started at point %i, stopped at %i.\n',istim1,istim2);
```

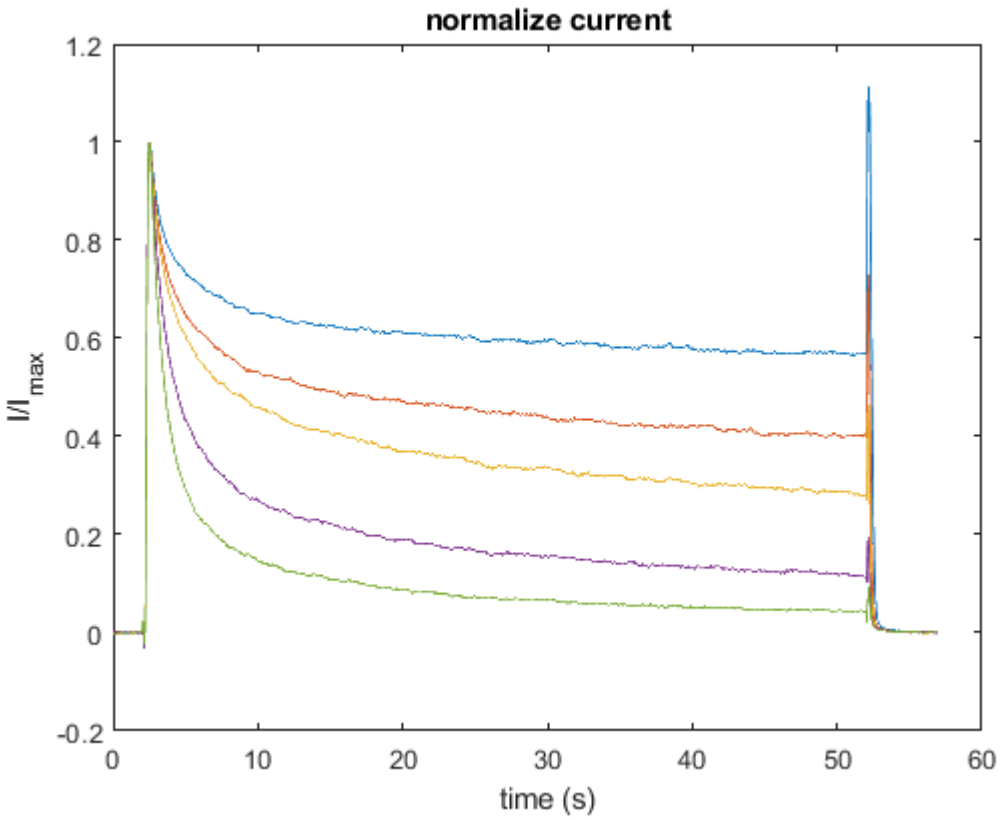
```
stimulus started at point 102, stopped at 2601.
```

Determine I_max, time of I_max and corresponding sample index

```
[imax,i_imax] = min(DataE53S1{istim1:istim2,2:end});
t_imax = time(i_imax);
i_imax = istim1 + i_imax - 1;
```

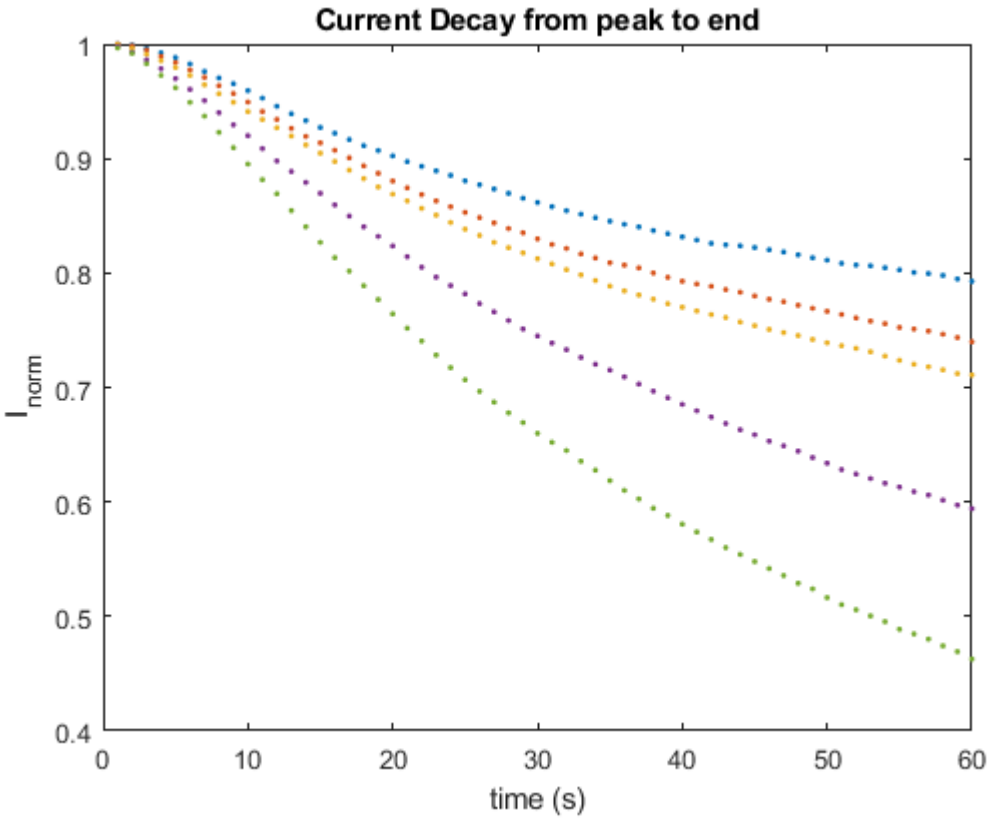
Normalize Data

```
In = DataE53S1{:,2:6}./repmat(imax,size(DataE53S1,1),1);
figure;
plot(time,In);
title('normalize current');
ylabel('I/I_{max}');
xlabel('time (s)');
```



Plot current decay

```
i_imax_max = max(i_imax);
figure;
idx = i_imax_max:istim2;
plot(In(idx,:),'.');
xlabel('time (s)');
ylabel('I_{norm}');
title('Current Decay from peak to end');
xlim([0 60]);
```



Fit Exponential Decay Models to Data

Prepare data

```
idx = i_imax_max+20:istim2; %cut first 20 data points after peak!
t = time(idx);
nobs = numel(t);
t = t - t(1); %adjust begin to zero
Y = In(idx,:); %1st 10 samples after max current are not considered
```

Apply lsqcurvefit():

```
% x0_temp = [.5 4 200 .5 .5];
% X0 = repmat(x0_temp,5,1);
% opts = optimoptions('lsqcurvefit', ...
%                     'Algorithm', 'levenberg-marquardt', ...
%                     'Display', 'final-detailed' ...
%                    );
% [x,resnorm,residual,exitflag,output] = lsqcurvefit(@(x,t)modelfun(x,t), ...
%                                                    X0(:), ...
%                                                    t,Y(:), ...
%                                                    [], [], ...
%                                                    opts ...
%                                                   );
% X = reshape(x,5,5);
% yfit = modelfun(x,t,nobs);
```

```
% Yfit = reshape(yfit,numel(t),5);
```

Apply fitnlm():

```
x0_temp = [.1 4 200 .5 .5];
x0_temp(1:3) = sqrt(x0_temp(1:3));
X0 = repmat(x0_temp,5,1);
%        tau1  tau2  tau3   a     s
fitx = [ false false  true false  true ];
Fitx = repmat(fitx,5,1);
Fitx(1,:) = true;

Coef_names = { 'tau1_1','tau2_1','tau3_1','a_1','s_1'; ...
               'tau1_2','tau2_2','tau3_2','a_2','s_2'; ...
               'tau1_3','tau2_3','tau3_3','a_3','s_3'; ...
               'tau1_4','tau2_4','tau3_4','a_4','s_4'; ...
               'tau1_5','tau2_5','tau3_5','a_5','s_5'  ...
             };
opts = statset('Display','final', ...
               'TolFun', 1e-8 ...
              );
M = fitnlm(repmat(t,5,1),Y(:), ...
           @(x,t)modelfun(x,t,nobs,X0,Fitx), ...
           X0(Fitx), ...
           'CoefficientNames',Coef_names(Fitx), ...
           'Options', opts ...
          );
```

```
Iterations terminated: relative change in SSE less than OPTIONS.TolFun
```

```
disp(M.Coefficients);
```

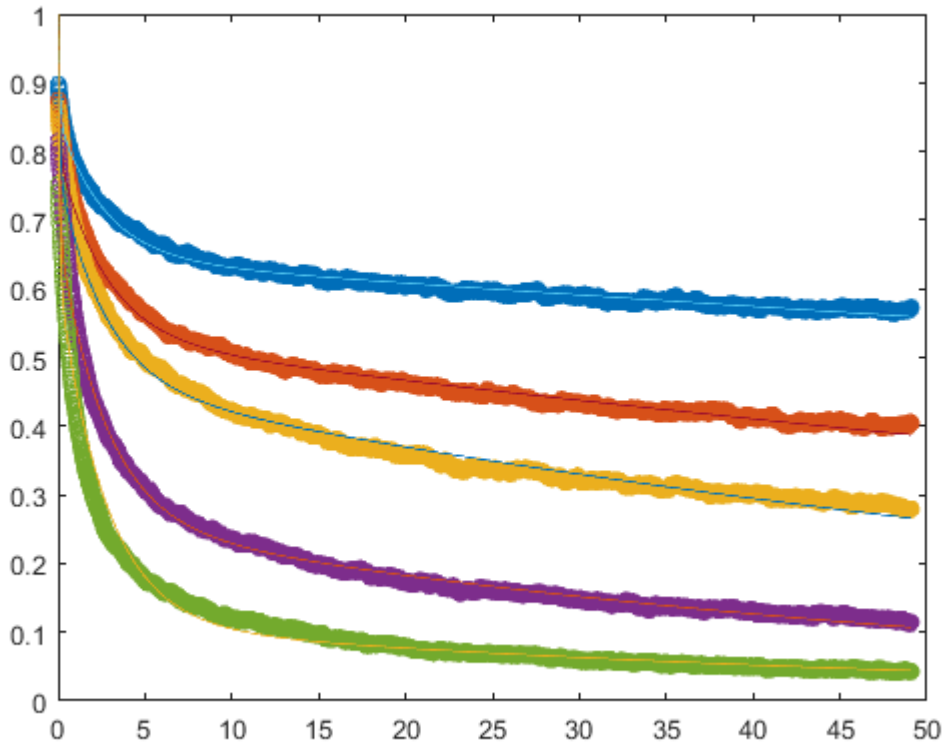
	Estimate	SE	tStat	pValue
tau1_1	0.29821	0.0027721	107.57	0
tau2_1	1.6402	0.0040347	406.52	0
tau3_1	18.67	0.087345	213.76	0
tau3_2	12.518	0.035919	348.5	0
tau3_3	9.4106	0.020196	465.97	0
tau3_4	7.3936	0.021924	337.24	0
tau3_5	7.2445	0.051836	139.76	0
a_1	0.4294	0.0016127	266.25	0
s_1	0.64422	0.00049605	1298.7	0
s_2	0.52998	0.0005418	978.18	0
s_3	0.46303	0.00059759	774.83	0
s_4	0.26301	0.00072284	363.85	0
s_5	0.11203	0.00078649	142.44	0

```
disp(M.Rsquared), disp(M.ModelCriterion);
```

```
    Ordinary: 0.9976
    Adjusted: 0.9976

     AIC: -7.8113e+04
```

```
     AICc: -7.8113e+04
      BIC: -7.8017e+04
     CAIC: -7.8004e+04
```

```
X = X0;
X(Fitx) = M.Coefficients.Estimate;
for j=2:5
   idx = ~Fitx(j,:);
   X(j,idx) = X(1,idx);
end

yfit = M.Fitted;
Yfit = reshape(yfit,numel(t),5);

figure;
plot(t,Y,'o');
hold on;
plot(t,Yfit,'-');
```



Concentration-Response Relations

```
M_hill_tau1 = fitnlm(c_ATO,X(:,3), ...
           @(p,x)p(1)+p(2)./(1+(p(3)./x).^p(4)), ...
           [7 10 1 -1], ...
           'Options', opts ...
```

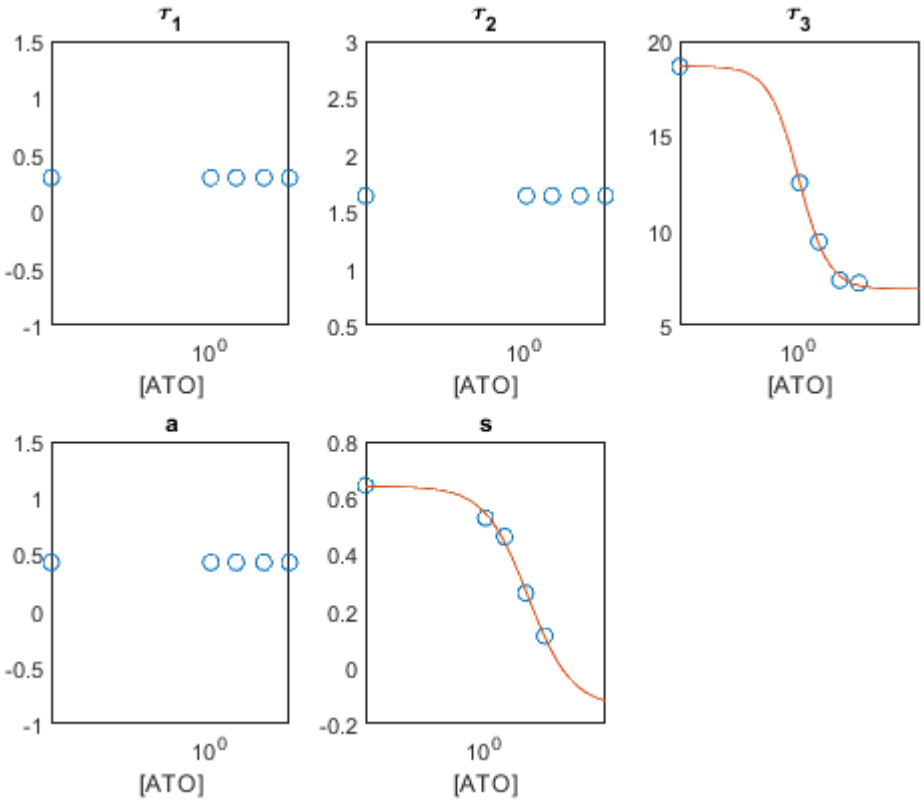
```
          );
```

```
Iterations terminated: relative change in SSE less than OPTIONS.TolFun
```

```
M_hill_s = fitnlm(c_ATO,X(:,5), ...
           @(p,x)p(1)+p(2)./(1+(p(3)./x).^p(4)), ...
           [.1 .55 2 -1], ...
           'Options', opts ...
          );
```

```
Iterations terminated: relative change in SSE less than OPTIONS.TolFun
```

```
cATO_fit = 10.^linspace(-3,3,80);
yfit_tau1 = predict(M_hill_tau1,cATO_fit');
yfit_s = predict(M_hill_s,cATO_fit');

figure;
subplot(2,3,1);
semilogx(c_ATO,X(:,1),'o');
title('\tau_1');
xlabel('[ATO]');
subplot(2,3,2);
semilogx(c_ATO,X(:,2),'o');
title('\tau_2');
xlabel('[ATO]');
subplot(2,3,3);
semilogx(c_ATO,X(:,3),'o');
hold on;
semilogx(cATO_fit,yfit_tau1,'-');
title('\tau_3');
xlabel('[ATO]');
subplot(2,3,4);
semilogx(c_ATO,X(:,4),'o');
title('a');
xlabel('[ATO]');
subplot(2,3,5);
semilogx(c_ATO,X(:,5),'o');
hold on;
semilogx(cATO_fit,yfit_s,'-');
title('s');
xlabel('[ATO]');
```



Local Function Definitions

```
function y = modelfun(x,t,nobs,X0,Fitx)
   X = X0;
   X(Fitx) = x;
   for j=2:5
       idx = ~Fitx(j,:);
       X(j,idx) = X(1,idx);
   end
   t = t(1:nobs);
   Y = zeros(nobs,5);
   for k=1:5
       p1 = exp(-t./X(k,1).^2);
       p2 = exp(-t./X(k,2).^2);
       p3 = exp(-t./X(k,3).^2);
       Y(:,k) = (X(k,4).*p1 + (1-X(k,4)).*p2).*(1-X(k,5)) + X(k,5).*p3;
   end
   y = Y(:);
end

function f = optimfun(x,t,y,nobs)
   yfit = modelfun(x,t(1:nobs));
   f = sqrt(sum((y - yfit).^2));
end
```