

Dynamic Data-based Modelling of Synaptic Plasticity: mGluR-dependent Long-term Depression

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Abstract: Recent advances have started to uncover the underlying mechanisms of metabotropic glutamate receptor (mGluR) dependent long-term depression (LTD). However, it is not completely clear how these mechanisms are linked and it is believed that several crucial mechanisms still remain to be revealed. In this study, we investigated whether system identification (SI) methods can be used to gain insight into the mechanisms of synaptic plasticity. SI methods have shown to be an objective and powerful approach for describing how sensory neurons encode information about stimuli. However, to the author's knowledge it is the first time that SI methods are applied to electrophysiological brain slice recordings of synaptic plasticity responses. The results indicate that the SI approach is a valuable tool for reverse engineering of mGluR-LTD responses. It is suggested that such SI methods can aid to unravel the complexities of synaptic function.

1 INTRODUCTION

Synaptic plasticity in general terms is the change of strength of synaptic connections between neurons. Long-term potentiation (LTP) and long-term depression (LTD), two extensively studied forms of synaptic plasticity, are characterised by a persistent increase and decrease of synaptic efficacy, respectively. Long-term synaptic modifications play a key role in the plasticity of behaviour, learning and memory (Kandel, 2001); (Malenka and Bear, 2004); (Neves et al., 2008); (Richter and Klann, 2009; Collingridge et al., 2010). This work focuses on metabotropic glutamate receptor (mGluR)-dependent long-term depression.

In spite of many research on mGluR-LTD [reviewed in (Massey and Bashir, 2007); (Bellone et al., 2008); (Collingridge et al., 2010); (Lüscher and Huber, 2010)], it is not completely clear how these mechanisms are linked and most likely several crucial mechanisms still remain to be revealed.

Most models are dynamical mechanistic models describing the considered system based on a priori knowledge of the system (Shouval et al., 2002);

(Nieus et al., 2006); (Manninen et al., 2010).

In recent years, more and more researchers advocate the use of a top-down (data-based) modelling approach in addition to an earlier mentioned mechanistic (or bottom-up) approach for improving the knowledge of biological systems (e.g. Jarvis et al., 2004); (Tomlin and Axelrod, 2005); (Tambuyzer et al., 2011). The power of the dynamical systems approach to neuroscience, as well as to many other sciences, is that we gain insight into a system without knowing all the details that govern the system evolution (Izhikevich, 2007).

In this study, we hypothesise that it is possible to uncover the underlying dominant processes of mGluR-LTD by applying mathematical system identification methods. This hypothesis resulted in 2 main objectives: (1) to quantify the dynamics of LTD responses for different experimental conditions using a discrete-time transfer function (TF) approach. The models describe the relation between the DHPG application (input) and the long-term depression responses (output); (2) to investigate whether system identification methods can be valuable to gain insight into the mechanisms of synaptic plasticity. Therefore, we examined whether

the estimated TF models allowed us to identify and quantify the major sub-processes involved in mGluR dependent long-term depression.

2 MATERIALS AND METHODS

2.1 Experiments

2.1.1 Animals and Brain Slice Preparation

Wistar rats (10-14 months old) were killed by cervical dislocation and the hippocampus was rapidly dissected out into ice-cold ($4\pm C$) artificial cerebrospinal fluid (ACSF), oxygen saturated with carbogen (95% O₂ / 5% CO₂). Transverse hippocampal slices (400 μ m thick) were prepared and placed into a submerged-type chamber, maintained at $33\pm C$ with carbogen saturated ACSF perfused at 2.4 ml/min by a peristaltic pump.

The animals were maintained and experiments were conducted in accordance with Institutional (KU Leuven), State and Government regulations.

2.1.2 Electrophysiological Recording

Synaptic responses were elicited by stimulation of the Schaffer collateral afferents using a teflon-coated tungsten electrode. A glass electrode (filled with aCSF, 1-4 M Ω) was used to record the evoked extracellular field Excitatory Postsynaptic Potentials (fEPSPs) in the CA1 region of the hippocampal slices. The slope of the fEPSP curves (mV/ms) was used as an indicator for the synaptic strength as described previously (Balschun et al., 2003). The stimulus intensity (μ A) was adjusted to elicit an fEPSP response with a slope 35% of the fEPSP slope maximum, determined by input/output curves.

A dataset was generated with a stimulation frequency of 0.033 Hz. Every generated data-point corresponded with a single stimulus. In total nine repetitions were performed resulting in 9 time series of fEPSP slopes.

2.1.3 Drug Application

After the brain slice preparation and the tuning of the electrode settings, the experiments started. First, there was a period of baseline recording (50 minutes) during which no drug was applied. After the baseline recording, metabotropic (mGluR)-LTD was induced in the rat brain slices by bath-application of dihydroxyphenylglycine (DHPG). The drug was applied for 2hours, in a concentration

of 30 μ M by the peristaltic pump.

2.2 Modelling

2.2.1 Dynamic Data-based Models

For the modelling, discrete-time Transfer Functions (TF) models were used. The models were single-input single-output (SISO) models. For this work, brain slices were exposed to a specific DHPG concentration to induce synaptic plasticity in the brain slices. The DHPG concentration (μ M) was used as input and the synaptic strength was the output (measured fEPSP slopes as percentage of the initial fEPSP slopes before drug application; see Figure 1). The dataset consisted of nine repetitions for the same experimental conditions.

The obtained responses (time series of fEPSP slopes) were averaged and the resulting mean response curve was used to estimate the TF models. A SISO discrete-time TF model can be described by the following general equation (Young, 1984):

$$y(k) = \frac{B(z^{-1})}{A(z^{-1})}u(k - \delta) + \xi(k) \quad (1)$$

where $y(k)$ is the output (synaptic strength); $u(k)$ is the input (DHPG concentration); k is the time for discrete time steps; δ is the time delay ($\delta > 0$); ξ is additive noise, a serially uncorrelated sequence of random variables with variance that accounts for measurement noise, modelling errors and effects of unmeasured inputs to the process. $A(z^{-1})$ and $B(z^{-1})$ are polynomials of the model parameters which can be written as:

$$\begin{aligned} A(z^{-1}) &= 1 + a_1 z^{-1} + \dots + a_n z^{-n} \\ B(z^{-1}) &= b_0 + b_1 z^{-1} + \dots + b_m z^{-m} \end{aligned} \quad (2)$$

Every polynomial is a function of z^{-1} , which is a backward shift operator that is defined as $z^{-1}y(k) = y(k-1)$. Finally, a_i and b_i are the model parameters. Here, n represents the order of the system.

Simplified refined instrumental variable (SRIV) algorithms were used for the identification and estimation of the model parameters (Young, 1984). All calculations were performed in Matlab using the Captain Toolbox (Taylor et al., 2007). Different numbers of denominator and numerator parameters (n and m ranging from 1 to 5) and different time delays (0 to 10) were investigated resulting in 275 (5x5x11) model structures. For each of these model structures, TF models were estimated.

Three criteria were used to select the best

models: R_T^2 values (Young, 1984), the Akaike Information Criterion (AIC; Akaike, 1974) and the Young Identification Criterion (YIC; Young, 1984). In addition to these three statistical criteria, each candidate model was also evaluated by visual inspection (Ljung, 1987). The three statistical criteria are described below:

$$R_T^2 = 1 - \frac{\hat{\sigma}_e^2}{\sigma_y^2} \quad (3)$$

$$\text{AIC} = \log_e(\sigma_e^2) + 2 \frac{h}{N} \quad (4)$$

$$\text{YIC} = \log_e \frac{\hat{\sigma}_e^2}{\sigma_y^2} + \log_e \{NEVN\}; \quad (5)$$

$$NEVN = \frac{1}{h} \sum_{i=1}^{i=h} \frac{\hat{\sigma}_e^2 \hat{p}_{ii}}{\hat{a}_i^2}$$

In these equations, $\hat{\sigma}_e^2$ refers to the variance of the residuals, $\hat{\sigma}_y^2$ is the variance of the output and h is the number of estimated parameters (i.e. $n+m+1$) in the parameter vector $\hat{\mathbf{p}}$ (i.e. $\hat{\mathbf{p}} = [a_1, \dots, a_n, b_0, \dots, b_m]$). N is the number of samples. \hat{p}_{ii} is the i^{th} diagonal element of the covariance matrix generated by the estimation algorithm and \hat{a}_i^2 is the square of the i^{th} parameter in the $\hat{\mathbf{p}}$ vector. R_T^2 is a statistical measure for the goodness of fit of the simulation response. AIC is partly dependent on the fit of the simulation but there is also a second component which takes into account the number of parameters, penalising the AIC value for relatively high order models. The YIC criterion is more complex and uses log terms so that improved models are indicated by increasingly negative values. The first term is a relative measure of how well the model explains the data. The second term relates to the conditioning of the instrumental variable cross product matrix and is a measure of potential over-parameterisation in the model. In particular, $\hat{\sigma}_e^2 \hat{p}_{ii}$ in equation (5) are the standard errors of the parameter estimates, with larger standard errors implying poorer YIC values. The TF models were validated by an autocorrelation test for the residuals and a cross correlation test between the residuals and the inputs (Ljung, 1987).

2.2.2 Identification and Quantification of Sub-processes

Higher order TF models ($n > 1$) can be described as a configuration of first order models ($n = 1$), which represent the dynamics of the sub-systems. For example, a second order model can be decomposed into two such first order TF models corresponding with three important types of coupling: a serial coupling, a parallel coupling or a feedback coupling (see Figure 1). Models with a model order higher than two result in more complex configurations, but are not required for the analysis in this article (as discussed later).

Based on such first order models, the dynamics of the subsystems could be quantified by means of their time constants. The time constant (TC) of a first order model can be determined as (Young, 1984):

$$TC = \frac{-\Delta k}{\ln(-a_1)} \quad (6)$$

Where Δk is the sampling interval and a_1 the denominator parameter. In practical terms the TC is the time taken for the output to reach 63% of its steady state value, in response to a step input.

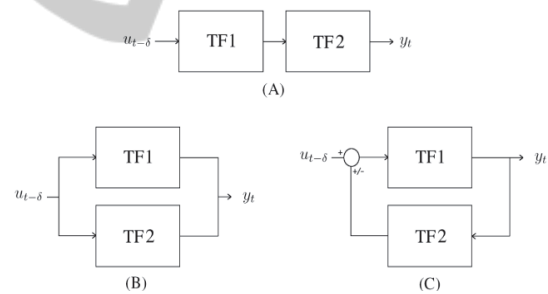


Figure 1: Possible configurations of two first order models. (A) Serial coupling. (B) Parallel coupling. (C) Feedback coupling.

3 RESULTS

3.1 Dynamic Analysis for Different Sampling Rates

Firstly, a first order model was calculated with an R_T^2 of 0.90 (see Table 1 and Figure 2). The corresponding time constant was 65 s (see equation 6), which strongly suggested the need for a sample rate of 0.033 Hz or higher to optimally represent the real underlying system (e.g. mechanisms of mGluR-LTD).

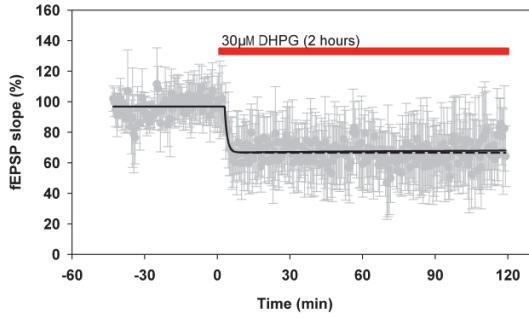


Figure 2: Measured mean LTD response curve +/-std (gray) with corresponding best first order model (dashed) and best second order model (black) (2 hours application of 30 μ M DHPG).

Table 1: Best first order model for mean LTD responses: parameters a_1 , b_0 with corresponding standard errors, SE, YIC, AIC, R_T^2 and time constant (TC).

a_1	SE(a_1)	a_2	SE(a_2)
-0.6299	0.0683	-0.3733	0.0684
YIC	AIC	R_T^2	TC
-5.352	-13.357	0.90	65 s

Secondly, we identified different higher models. The best third, fourth and fifth order models were excluded because of over-parameterisation. The best higher order model was a second order model with $n = m = 2$ (see Table 2).

Table 2: Best second order model for mean LTD responses: parameters a_1 , a_2 , b_0 , b_1 with corresponding standard errors, SE, YIC, AIC and R_T^2 .

a_1	SE(a_1)	a_2	SE(a_2)
-1.6023	0.0661	0.6037	0.0644
b_0	SE(b_0)	b_1	SE(b_1)
-0.3957	0.0636	0.3944	0.0655
YIC	AIC	R_T^2	
-5.075	-20.824	0.89	

For this model, the R_T^2 value was 0.89 and the fit was similar to the one of the first order model (see Figure 2). One pole was close to unity, indicating an integrator effect. In addition, the sum of the numerator parameters of the second order TF model was almost equal to zero ($b_0 + b_1 = -0.0013$; see Table 2), which could imply a switch-like effect of the DHPG input on the synaptic efficacy (cf. $k=0$ in Figure 2). This effect can be shown starting from $x(k)$, the noise free output of the general TF model equation:

$$x(k) = 1.602x(k-1) - 0.604x(k-2) - 0.396u(k) + 0.394u(k-1) \quad (7)$$

The synapses react especially at the start of the drug application for which $u(k) \neq u(k-1)$ (e.g. for $k=0$ in

Figure 2). When the applied drug concentration is steady, the effect of the drug will saturate and there will be a negligible effect on the synaptic outputs since $0.396u(k) \approx 0.394u(k-1)$ for $u(k) = u(k-1)$.

3.2 Model-based Identification of Dominant Sub-processes

The accurate second order model suggested that there are two coupled dominant processes which underlie mGluR-LTD. From a mathematical point of view, two possible configurations of first order models were suggested: a parallel circuit and a feedback circuit (see Figure 1). The serial configuration was mathematically impossible for this model structure ($n = m = 2$; see Table 2) and could be excluded. The model characteristics of the first order models for the feedback and parallel solution are shown in Table 3.

Table 3: First order models, TF1 and TF2, obtained after decomposing the second order model for parallel and feedback configuration (see Figure 1 and 2).

TF1			
Configuration	a_1	b_0	TC
Parallel	-0.9965	0.0002	24 hrs
Feedback	-0.6058	-0.3958	60 s
TF2			
Configuration	a_1	b_0	TC
Parallel	-0.6058	-0.3959	60 s
Feedback	-0.9967	-0.0006	25 hrs

4 DISCUSSION

Recent advances of imaging techniques have made possible to visualise and quantify synaptic changes on a time scale of months or years. These studies have shown that synapses have many dynamic properties that appear (and disappear) repeatedly over time (Hou et al., 2006); (Kondo and Okabe, 2011). Therefore, dynamical analyses of synaptic plasticity can highly contribute to fully comprehend the underlying synaptic mechanisms. In many studies, electrophysiological brain slice recordings are used to measure the synaptic strength and to analyse the different forms of synaptic plasticity. However, in most studies the fEPSP recordings are only statically analysed and the fEPSP slopes are compared for only one time point or a limited number of time points after the induction of LTD or LTP. To the authors' knowledge, it is the first time that fEPSP slopes of mGluR-LTD responses are dynamically described using TF models.

The second order model could be decomposed into two first order models and suggest that two major sub-processes underlie mGluRLTD: one slow and one fast sub-process (see Table 3). A parallel circuit and a feedback circuit were suggested as candidate configurations of these two sub-processes.

Possibly, the fast time constants describes the fast processes immediately after induction mediated by activation of the ERK/MAPK pathway and tyrosine dephosphorylation (e.g. of GluR2) with the tyrosine phosphatase striatal-enriched tyrosine phosphatase (STEP) as a main player.

The slow time constant, in contrast, is likely to reflect structural changes, for example in spine number and morphology, that were demonstrated in other models of synaptic plasticity to be protein-synthesis-dependent and to occur on a time-scale of hours (Fukazawa et al., 2003; Raymond, 2007). Many studies show the presence of feedback loops in cellular control systems (Mitrophanov & Groisman, 2008). Neural mechanisms are known to contain many non-linearities, but our modelling results confirm other studies in which discrete-time linear system identification techniques were successfully used for modelling brain signals (e.g. Liu et al., 2003; Westwick et al., 2006; Behrend et al., 2009).

5 CONCLUSIONS

Discrete-time TF models are interesting to investigate mGlu receptor-dependent LTD, because of their computational and conceptional simplicity and since they are able to combine the advantages of a data-based approach (accurate models) with a mechanistic approach (meaningful parameters). This study suggests that the dynamic data-based modelling approach can be a valuable tool for reverse engineering of mGluR-dependent LTD responses. Moreover, this approach can also be extended to other forms of LTD and LTP using other induction protocols as input for the TF models. It is expected that such system identification methods can aid to unravel the complexities of synaptic function and its role in disease.

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