Challenges in biological time series forecasting using neural networks

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Abstract

Predicting the future development of time series is of interest in different areas of computational biology. The time series in biological systems exhibit challenging characteristics such as chaotic or stochastic behavior. In this report, time series forecasting and generation is done on several kinds of biological time series using deep neural networks. We compare classical multi layer perceptrons with recurrent and convolutional architectures. In our evaluation, we identify challenges and limitations of neural networks for these tasks, and compare different architectures of deep neural networks with regard to their performance. We conclude that the configuration of the optimization algorithm has strong impact on the results, independent of the architecture. The nature of the noise in the data has also strong influence. We also show that a generation of stochastic time series is not possible using deterministic neural networks, because only the mean of the probability distribution can be estimated. The code used in our experiments can be found on GitHub.

1 Introduction

In various kinds of diseases, it is important to choose the correct treatment at the current time point. Since the human body is too complex to be described directly using mathematics, special features are modeled with mathematical systems such as the Mackey-Glass equations for respiratory and hematopoietic diseases [MG77]. These models make use of available data about previous information in order to reduce the uncertainty under which a decision is made. This is especially important when the consequences of a decision are severe, for example the decision of breast cancer treatment after radiation. This particular problem can be addressed by using a stochastic differential equation, as done by Oroji et al [OOY16].

In different kinds of biological models, even chaotic behavior is observed. The Mackey-Glass equations possess chaotic behavior for certain choices of their parameters, as shown by Farmer [Far82]. That means that even small measurement errors of the initial state lead to exponentially increasing errors of the time series prediction. Because of that, it is important that the time series prediction should be as robust as possible against noise.

This gets important in particular because biological data cannot be measured without the presence of noise. In this report, we show that different kinds of noise assumptions can impact the results of time series prediction. We evaluate all our investigated problems with regard to the popular independent and identically distributed (i.i.d.) random noise as well as noise from a discretized Wiener process. Since mathematical models of biological systems cannot describe their characteristics perfect and error-free, it is assumed that the latter type of noise is more realistic. But unfortunately this kind of noise increases the difficulty of time series prediction, even for simple mathematical functions, as seen in Section 3.1.

The remaining report is structured as follows. First, we perform proper time series prediction on the sinus function and show how different noise models impact the prediction ability of our network models. After that, we show how different levels of chaos impact the possibility to forecast the development of time series at the example of the Mackey-Glass time series. We show how the variance and the type of noise impacts the possibility to predict deterministic chaotic time series at the example of this time series. Last but not least, we report fundamental limitations of neural networks to approximate stochastic time series at the example of biological oscillators.

2 Methods

In our analysis, we use three different architectures and neural networks and optimize their hyperparameters for the respective use case. Since Hornik $et\ al.$ have shown that multi-layer perceptrons (MLP) are universal function approximators [HSW89], we evaluate this architecture with varying number of hidden nodes.

After that, we investigate the strength of improvement of using a recurrent neural network. This type of neural network has already been applied to time series prediction [CMA94], but suffers from the vanishing gradient problem when capturing long-term dependencies in a sequence. Because of that, we decide to evaluate only the Long Short-Term Memory (LSTM) network architecture [HS97], which was successfully applied in various time series prediction tasks like anomaly detection [MVSA15], stock price [FK18] and protein disorder prediction [HYPZ16].

In the last years, convolutional neural networks (*CNN*s) have improved the results in image classification [KSH12] and other computer vision tasks. A *CNN* learns features from the data in a hierarchical way, for example combining pixels to edges, edges to more complex forms etc. until a high-level classification can be done. The large success in computer vision has inspired researchears in time series prediction to also apply *CNN*s [CCC16, BBO17], so we also evaluate this architecture in our analysis. The same way as images are composed of hierarchical features (e.g. a face consisting of eyes, that consist of certain edges etc.) we assume that similar hierarchies of features can be found in time series data.

The loss is measured using the classical mean squared error (MSE) or the root mean squared error (RMSE), because López-Caraballo et al. [LCSL+16] use this error function to compare various other neural network approaches for Mackey-Glass time series prediction. This function is computed in Equation 1.

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{n}}$$
 (1)

In order to train our models, we apply the Adam optimizer [KB14]. This famous

optimization algorithm (more than 20.000 citations in less than 5 years) is commonly used to train neural networks and improves the stochastic gradient descent algorithm. Other optimization algorithms are not considered in order to keep the hyperparameter tuning feasible.

We use two different types of noise. First, we consider i.i.d. gaussian noise which is added to the underlying function f(t) at each point of time t, as seen in Equation 2. The other type of noise is a discretized Wiener process, as given in Equation 3. This kind of stochastic process is used in various areas, for example to study Brownian motion in Physics. For more details about Wiener processes, refer to Schilling $et\ al$ [SP14].

$$\forall t: \quad x(t) = f(t) + y, \quad y \sim \mathcal{N}(0, \sigma^2)$$
 (2)

$$\forall t : x(t) = f(t) + y(t), \ y(t) = y(t-1) + y, \ y \sim \mathcal{N}(0, \sigma^2), \ y(0) = 0$$
 (3)

All implementations are done using the Python programming language in version 3.6.7. The time series data is created and loaded in the numpy framework in version 1.16.1. In order to train the neural networks both fast and elegant, we use the keras framework (version 2.2.4) with the tensorflow backend in version 1.13.1. The reason for this choice is the tight integration between keras and numpy that simplifies and increases the speed of our software development. Before running the experiments, the random number generator of numpy is set to the seed 0 to ensure reproducibility of data generation. The time series data for the biological oscillator is generated using gillespy [ADHP16], which only works with Python in version 2. For this application, the version 2.7.15 of Python is used.

3 Evaluation

3.1 Time series forecasting of periodic functions

In the first part of the analysis, we analyze the capability of different neural network architectures to perform time series prediction on the periodic sinus function. This task can be considered simple, because the different parts of the sine wave occur multiple times in the data. It is therefore interesting how robust the network architectures are with regard to different kinds of noise.

In this problem, we apply a large grid search over several parameters given in Table 1. All models are trained using the Adam optimizer and 10 time sequence entries are used to predict 1 directly consecutive point. These assumptions are made in order to keep the grid search feasible. For training, testing and validation, a range from 0 to 6π is used. The data is split equally between the datasets, the first third used as the training and the second third used as the validation set. Expressed more formally, we provide information about the last 10 time sequence points to the network and want to predict the next point, as given in Equation 4. That is, we want to estimate x(t) with a function $F(x(t), x(t-1), \dots, x(t-9))$ that is approximated using a neural network.

$$\hat{x}(t+1) \approx F(x(t), x(t-1), \cdots, x(t-9))$$
 (4)

Parameter	Values
Number of hidden nodes	[5, 10, 20]
std (σ) of noise	[0, 0.01, 0.1]
Noise type	["iid", "Wiener process"]
Learning rate	[0.001, 0.01, 0.1]
Epochs of training	[10, 100, 500]
Neural network architecture	["MLP", "LSTM", "CNN"]

Table 1: Parameter combinations used for the grid search. Each possible value of each parameter is combined with each possible value of each other parameter. Note that the *CNN*s are evaluated with 1, 2, or 3 hidden layers of with 8 filters instead of the given numbers of hidden nodes.

Architecture	Average MSE
MLP	0.00285
LSTM	0.00066
CNN	0.07583

Table 2: Average MSE over all applied neural networks aggregated by the neural network architecture type.

As we expected based on our literature review, the LSTM yielded lowest test error on the noise free time series data as seen in Table 2. We use the MSE here and evaluate on the test error because we are interested in generalisation capability of the neural networks, which cannot be evaluated based on the training error. After investigating the high error for the CNN architecture, we discover that this architecture needs a lower training rate than the LSTM architecture to yield good results – the learning rate of 0.1 is too high and ruins the results as seen in Table 3.

Next we investigate the influence of the type of noise and the standard deviation of the noise on the results based on our grid search. The average error is strongly impacted as seen in Table 4. We see that a higher standard deviation (σ) increases the test error. But it seems that the neural networks are less capable of filtering noise from a Wiener process, and for a high σ of this type of noise completely lose the ability to approximate the underlying sinus function on the first look. A further analysis of the used networks architectures shows that this is merely caused by inluding CNNs trained with learning rate 0.1. After excluding them, the test error goes down to a high but reasonable value.

In Figure 1, we see the best neural network found using the large grid search for a

Learning rate	Average MSE (CNN)	Average MSE (LSTM)
0.1	0.227052	$5.391024 \cdot 10^{-5}$
0.01	0.000155	$8.129514 \cdot 10^{-5}$
0.001	0.000159	0.000276

Table 3: Comparison of the average MSE when training CNN and LSTM architectures. We see that the LSTM can be trained using higher learning rates.

Type of noise	MSE	$MSE (\sigma = 0.01)$	$MSE(\sigma = 0.1))$
i.i.d noise	0.015	0.008	0.022
Wiener process	24.153	0.0524	48.254 (1.322)

Table 4: Average MSE aggregated by the type of noise and the noise standard deviation. To ensure the results do not depend on the network architecture, the mean value of the MSE is taken across all configurations and network architectures evaluated in the grid search.

Noise type (standard deviation)	Net type	Epochs	Hidden Units	L.R.
no noise	MLP	500	5	0.001
i.i.d. (0.01)	LSTM	500	5	0.01
i.i.d. (0.1)	LSTM	100	5	0.001
Wiener (0.01)	CNN	500	1 layer	0.01
Wiener (0.1)	MLP	500	10	0.001

Table 5: Best performing neural network architectures for different noise settings. The LSTM are well suited to the i.i.d. distributed Gaussian noise, while the other architectures should be used for noise from a Wiener process.

noise free time series. The approximation is remarkably accurate and no deviation can be found. If we add different kinds of noise, the grid search is still able to find suitable architectures, as seen in Figure 2. In Figure 3 we demonstrate that only a few outliers caused the average error for Wiener process noise with high σ to increase so strongly.

After investigating the architectures of the best neural networks in Table 5, we conclude that LSTM networks are best suitable to situations in which i.i.d. distributed noise occurs. But also a classical MLP architecture performed best in presence of high Wiener noise, while for a small amount of Wiener noise, the CNN architecture is advantageous. From the grid search, we conclude furthermore that the default parameters in the optimization algorithms can be improved in various cases. The longest training is not always delivering the best results, which indicates the importance of the Early Stopping technique. Using the grid search on a various number of parameters, it was possible to find a suitable architecture for each of the considered situations.

3.2 Mackey-Glass time series forecasting

In order to model diseases related to dynamic respiratory and hematopoietic diseases, Mackey et al. proposed the Mackey-Glass equations, a kind of first-order nonlinear

Architecture	Noisefree data	i.i.d. noise	memorizing noise
MLP	0.0021	0.0249	0.0174
LSTM	0.0021	0.0127	0.5554
CNN	0.0021	0.0136	0.0234

Table 6: Validation loss of different neural network architectures for time series prediction on the sinus function stated in RMSE.

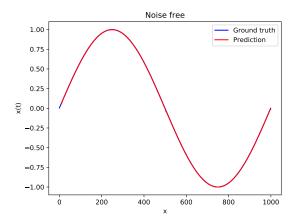


Figure 1: Demonstration of grid search results. For the noise free case, a nearly perfect approximation is achieved. The figure uses a MLP architecture, that contains 1 hidden layer with 5 neurons and is trained for 500 epochs with a learning rate of 0.001.

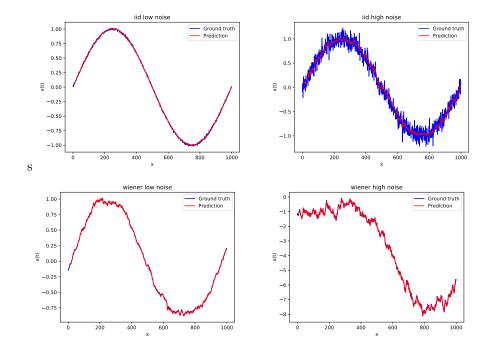


Figure 2: Demonstration of grid search results. The low noise has a standard deviation of $\sigma=0.01$ and the high noise uses $\sigma=0.1$, independent of the type of noise. Both predictions for i.i.d. noise are obtained using LSTM networks. The low variance noise from the Wiener process is best approximated using a CNN, while a MLP architecture shows best results for the high variance noise from the Wiener process. For details refer to Table 5.

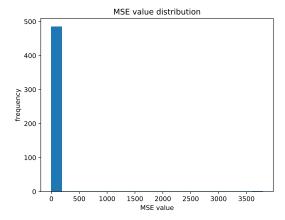


Figure 3: Demonstration of grid search results. A few networks with high test error have to be considered during the evaluation to get more robust interpretations. The majority of trained networks yield smaller test error values.

differential delay equations to model the number of white blood cells over time [MG77]. The solutions to these equations given in Equation 5 exhibit chaotic behavior under certain conditions [Far82]. For fixed parameters $a=0.2,\,b=0.1$ and c=10 this system has a stable fixed point attractor for $\tau<4.53$. With increasing delay time, the system gets less stable. For delay times of $4.53<\tau<13.3$ there is a limit cycle attractor whose period raises for $13.3\le\tau\le16.8$. For delay time $\tau>16.8$ the system shows chaotic behavior.

$$\frac{dx}{dt} = \frac{a \cdot x(t-\tau)}{1 + x(t-\tau)^c} - b \cdot x(t) \tag{5}$$

By using the Euler method to discretize the Mackey-Glass time series shown in Equation 6, we can see that the chaotic behavior gets stronger for increasing $\tau > 16.8$. In Figure 4, we simulate the solution of the Mackey-Glass time series for slightly different initial conditions. It is clearly visible that for $\tau = 17$, the time series diverges slower than for $\tau = 25$. In the phase plot in that figure we can see that the trajectory of the time delay $\tau = 17$ looks still similar to the non-chaotic trajectory of the time delay $\tau = 15$. But for $\tau = 25$, the chaos is so strong such that no similarity to the non-chaotic trajectories can be recognized.

The first approach to predict the short-time behavior of chaotic time series was done by Farmer et~al. who proposed a local approximation technique [FS87]. After improval of predictions using support vector machines by Müller $et~al.~[MSR^+97]$, the focus in research shifted towards artifical neural networks which enabled even better predictions. Two of the latest developments are the usage of Wavelet Networks [AZ13] and particle swarm optimization [LCSL^+16].

$$x(t+1) = x(t) + \frac{\beta x(t-\tau)}{1 + x^{n}(t-\tau)} - \gamma x(t)$$
 (6)

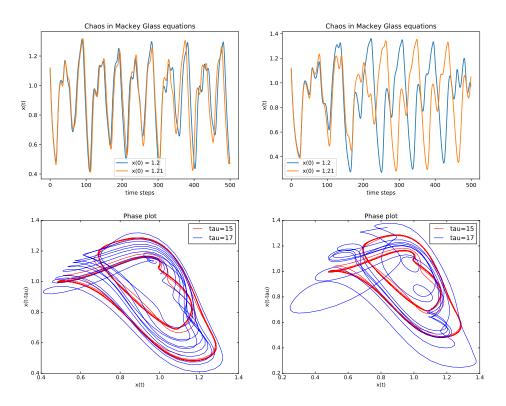


Figure 4: Influence of time delay parameter τ on the chaotic behavior of the Mackey-Glass equation. The top left side of the figure uses $\tau=17$, the right side $\tau=25$. The phase plot for $\tau=17$ shows additionally the phase plot for $\tau=15$ to visualize the similarity with a time series which is not chaotic, but has a limit cycle attractor instead.

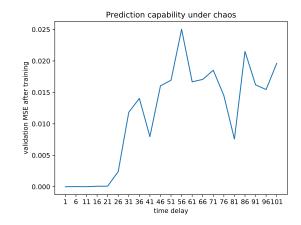


Figure 5: Validation error of the *LSTM* network for different time delay values τ of the Mackey-Glass equation. The error increases strongly for values of $\tau > 20$, indicating a strong chaotic behavior from this point.

In accordance with the approach used by López-Caraballo $et\ al.\ [LCSL^+16]$, we predict x(t+6) based on the information of the time series points in x(t), x(t-6), x(t-12), and x(t-18). We investigate how an increase in chaotic behavior impacts the prediction capability of the different neural network architectures. The results for the LSTM are depicted in Figure 5. For this plot, a 2-layer LSTM architecture is used, using 10 hidden nodes in the LSTM layer, followed by a feedforward layer to sum up for the output value. The first 500 time points of the time series are used for training, the 500 following points for validation. Additional 500 points are not used during the training procedure at all and form the test set. For training our models, we train the models for 100 epochs. The learning rate of 0.01 is used for the Adam optimizer, because it outperforms the default learning rate in this situation.

It can be seen that for non-chaotic solutions of the Mackey-Glass time series the model is able to predict precisely, and that for values of $\tau > 20$ the chaotic behavior is strong enough to impact the prediction. We explain the low error for $\tau = 21$ in the ability of the network to compensate for the amount of chaos up to this point.

In the next step, we compare our MLP, our LSTM and our CNN architectures with the results stated by López-Caraballo $et~al.~[LCSL^+16]$ in Table 7. We compare our results with a linear model, a cascade correlation neural network and a radial basis function (RBF) neural network additional to their approach to combine an artificial neural network (ANN) with particle swarm optimization (PSO). By using the ReLU (Rectified Linear Unit) activation function and two hidden layers with 32 and 16 nodes, respectively, we outperform the backpropagation network reported by López-Caraballo et~al. with our MLP architecture. From our considered models, the CNN achieves the lowest RMSE value and allows for accurate prediction, both for validation and for test data as seen in Figure 6. This CNN uses three convolutional layers with 1D convolutions, kernel size of 3, "same" padding and 8 filters each. A classical feedforward layer without activation function is used to extract the output value for the time series

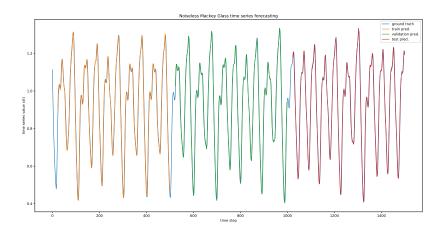


Figure 6: The prediction of the noisefree Mackey-Glass time series using a *CNN* with 3 hidden layers. The precise predictions for training, validation and testing points show the accurate approximation of the chaotic time series.

Method	$RMSE_{x(t+6)}$
Linear model	0.5503
Cascade correctation NN	0.0624
$proposed\ LSTM$	0.0131
$proposed\ MLP$	0.0125 (vs. 0.0262 [LCSL ⁺ 16])
RBFNN	0.0114
$proposed\ CNN$	0.0075
$ANN + PSO [LCSL^{+}16]$	0.0053

Table 7: Mackey-Glass time series forecasting results using different neural network architectures.

prediction. We avoid overfitting successfully, since the test data of the chaotic time series was never presented to the neural network, but is predicted accurately.

The LSTM employs 10 LSTM nodes, followed by a feedforward layer to sum up the results. A variety of other layer configurations has been applied on the problem, but all consistently perform worse than the other neural network architectures. We assume that the chaotic behavior of the time series confuses the LSTM which is trying to account for temporal dependencies between the time series points.

Now we apply noise on the Mackey-Glass time series to account for the imperfect data typical for biological measurements. The results for these experiments are stated in Table 8. We see that an increased standard deviation of the added noise increases the test error, measured in RMSE. This applies to all neural network architectures.

We interpret the results of Table 8 as the neural networks are capable of dealing with a certain amount of noise. For example the CNN has approximately 9 times higher error rate when increasing the standard deviation of the Wiener process from

Architecture	noise type	σ	RMSE
CNN	iid	0.01	0.0196
CNN	iid	0.1	0.0806
CNN	wiener	0.01	0.0242
CNN	wiener	0.1	0.2172
MLP	iid	0.01	0.0249
MLP	iid	0.1	0.0949
MLP	wiener	0.01	0.0348
MLP	wiener	0.1	0.2162
LSTM	iid	0.01	0.0432
LSTM	iid	0.1	0.0862
LSTM	wiener	0.01	0.0347
LSTM	wiener	0.1	0.2044

Table 8: Results of the Mackey-Glass time series forecasting using different types of neural networks, noise levels and types.

0.01 to 0.1.

But more interestingly, the negative effect of the noise is stronger if the noise generated from a Wiener process, i.e. if the effect of the noise in time step t impacts the time series in time step t+1. We explain this with an increase in chaotic behavior induced by this type of noise to the Mackey-Glass time series. Since chaotic time series by definition deviate exponentially based on small variations in the initial conditions, it seems logical that this divergence is increased by introducing perturbations of the time series in every time step.

3.3 Biological oscillator time series forecasting

The next section deals with time series generation of biological oscillators, as described by Novak *et al* [NT08]. For different aspects of cell physiology, e.g. the DNA synthesis, this kind of oscillators can be observed. Novak *et al.* show that oscillations in simple ODEs can be produced by incorporating an explicit time delay [NT08], similar to the Mackey-Glass equations [MG77].

Recently, Strömstedt et~al. analyzed the capability of neural network architectures to model stochastic time series [SSH18] at the example of time series produced according to the characteristics of Novak $et~al~[{\rm NT08}].$ In this section, we reproduce their results for the LSTM architecture and state fundamental limits for neural networks to approximate stochastic time series.

The gillespy framework is used to model a stochastic reaction system with 2 states, described in Equation 8. One protein X is produced more the less of the other protein Y exists. X and Y are both continuously reduced but Y gets reduced stronger for smaller values of Y in a non-linear way. A set of 6 parameters $(k_{dx}, k_t, k_{dy}, a_0, a_1, a_2)$ is used to parametrize the system.

Processor Intel(R) Core i5-7200U CPU @ 2.50GHz RAM 7859 MB

Table 9: Hardware configuration used in experiments.

$$\frac{dX}{dt} = \frac{1}{1+Y^2} - k_{dx} \cdot X \tag{7}$$

$$\frac{dX}{dt} = \frac{1}{1+Y^2} - k_{dx} \cdot X \tag{7}$$

$$\frac{dY}{dt} = k_t \cdot X - k_{dy} \cdot Y - \frac{Y}{a_0 + a_1 \cdot Y + a_2 \cdot Y^2}$$

The motivation for using neural networks to generate time series is the computational expensiveness of analytical solutions like the Gillespie algorithm [Gil77]. The runtime of an experiment on our hardware (see Table 9 for details) takes more than 6 seconds runtime to simulate this biological oscillator with two states for 100 time steps (yielding only one trajectory of the stochastic system). This makes grid search approaches on the large number of parameter combinations intractable. Using the 2layer LSTM approach, predictions for short time series can be done in less than 0.2 seconds on our hardware.

The goal here is to train a LSTM based model to convert a set of input parameters into a time series. The first LSTM layer takes 7 input values and transforms them into n sequences of 7 values, with n being the desired length of the output sequence. The second LSTM layer takes this intermediate result and converts it to a sequence of length n.

The analysis of the resulting time series as depicted in Figure 7 shows the general limitation of using a deterministic neural network for predicting a stochastic time series. For one possible parameter choice for the biological oscillator, the analytical solution was computed under 100 (stochastic) trajectories. After that, the network was trained to predict the time series based on the (unchanged) parameters. We see that the short-term predictions are accurate and have the same magnitude as the ground truth signal – but the more time steps are simulated, the larger is the difference between the ground truth trajectories due to stochasticity. In other words, the neural network predicts the mean of the signals and the amplitude decreases due to the increasing variance of the signal over time. It should be noted that the trends in the time series are still recognized, just with a smaller amplitude.

4 Conclusion

In this report, we investigate time series forecasting using neural networks. By applying a grid search on the time series forecasting of a continuous function, we find suitable architectures to produce accurate predictions for all considered types of noise. We discover that it is necessary to vary the configuration of the optimization algorithm w.r.t. the learning rate in order to find the optimal results. Furthermore, we applied neural networks to predict the chaotic Mackey-Glass time series. We can show that the prediction gets more challenging for the neural network with a higher delay parameter τ , which strengthens chaotic characteristics. When applying noise from a Wiener process,

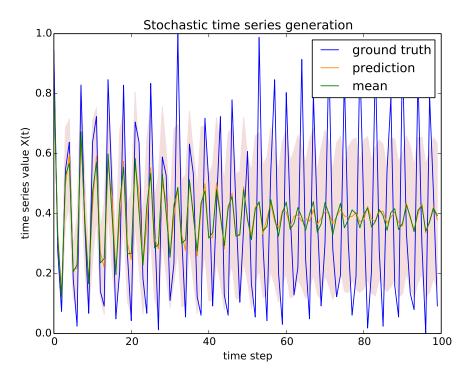


Figure 7: Prediction of stochastic time series using deterministic LSTM network. Sampled ground truth data are unseen for the network. Mean computed on all stochastic trajectories. The standard devation increases from the given starting point, because the stochastic trajectories change their values in different ways over time.

the error rate of the prediction increases strongly. The Wiener process perturbates the chaotic system and influences the subsequent steps of the time series, which enlarges the chaotic characteristics of the time series. Last but not least, we show at the example of biological oscillators that it is not possible to generate stochastic time series based on a set of scalar parameters with a deterministic neural network. The neural network approximator can only predict the mean of the probability distribution generating the noise, and therefore be used to predict trends in the time series. But since the amplitude declines below the level of the original time series, some features like spikes can not be generated.

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