

Noise from in-silico Biology: A Statistical Perspective

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Box 1: A stochastic approach

Computational models and simulation algorithms are commonly applied tools in biological sciences.

Among those, discrete stochastic models and stochastic simulation proved to be able to effectively capture the effects of intrinsic noise at molecular level, improving over deterministic approaches when system dynamics is driven by a limited amount of molecules.

The study of biological systems through discrete state-space stochastic models is a powerful tool that provides a rigorous conceptual framework for capturing in unambiguous executable format the available information, determining dynamic evolution and predicting the observed behavior of biological systems under diseases scenarios, mutations or drug induced perturbations.

It becomes necessary then to develop methods and tools able to manage the information derived from stochastic simulation results.

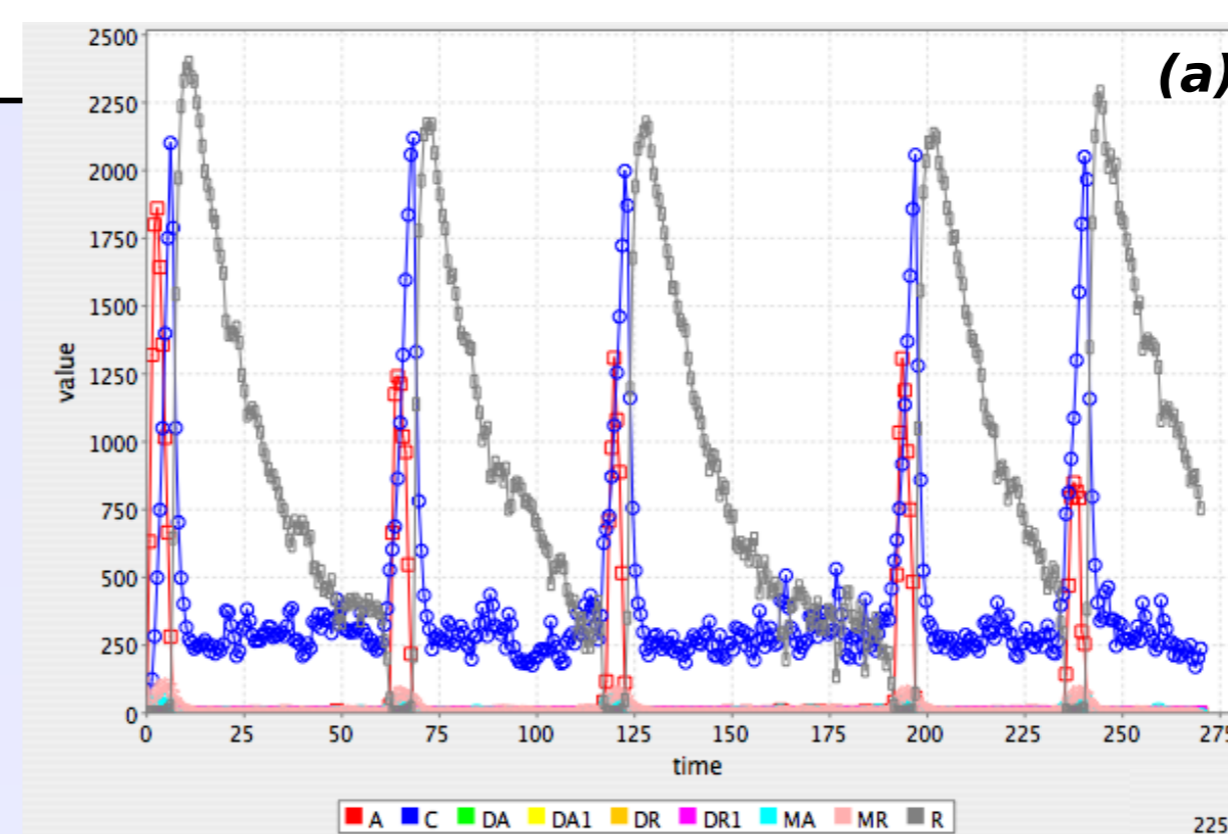
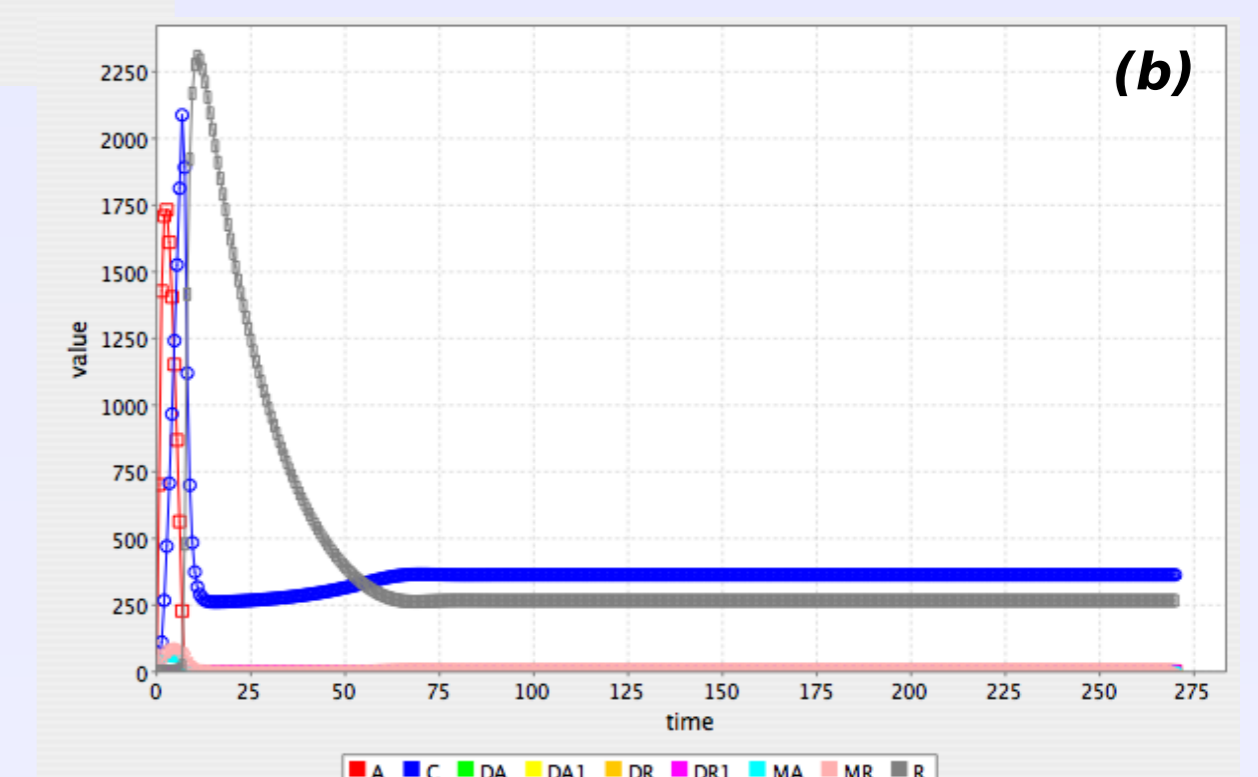


Figure 1. Does it oscillates or not?

Stochastic (a) and deterministic (b) simulations of an oscillatory biological system [1]. Under specific reaction rate constants stochastic simulations show oscillations, while deterministic simulations do not oscillate.



Box 2: Independent Component Analysis

Independent Component Analysis (ICA) is a member of the class of blind source separation methods and consists of recovering unobserved signals (the sources) from several observed mixtures.

Within the linear ICA model we observe n mixtures x_1, x_2, \dots, x_n of h unknown source signals s_1, s_2, \dots, s_h (the independent components), and a mixing relationship holds, such that: $x = As$ where A is the unknown mixing matrix.

ICA computes an estimate s^* of the original signals as much statistically independent as possible.

We use ICA for multi-run stochastic simulations analysis. With ICA we are able to decompose k stochastic simulations in 2 components: one representing the major mode of behavior of the system, and the second one representing the noise.

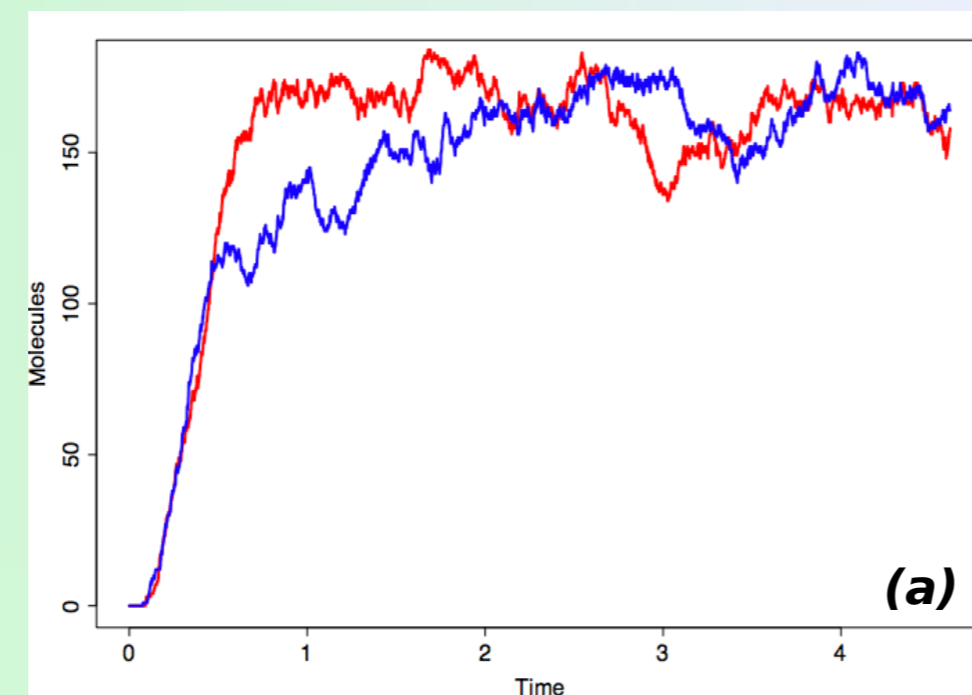
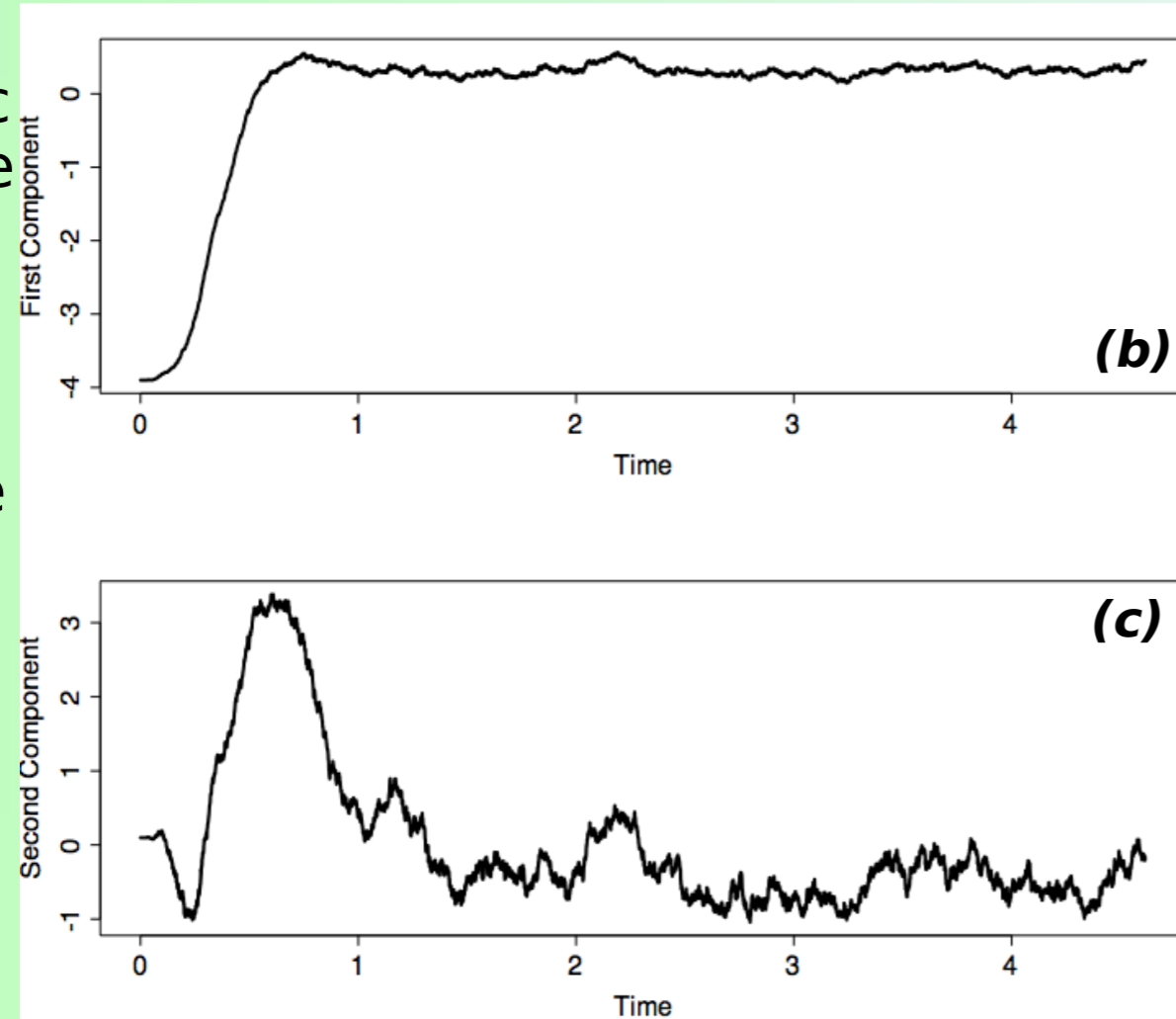


Figure 2. Independent Component Analysis for multi-run stochastic simulations

(a) Two stochastic simulations of the MAPK doubly phosphorylated molecule from the MAPK signaling cascade [2] (stochastic model developed in BlenX [3]). Applying ICA (here on 20 simulations) we derive 2 components: the major mode of behaviour (b) and the noise caused by stochastic fluctuations (c).



Box 3: Other approaches and future work

Statistical time regression models may give insights into stochastic noise effects.

Starting from a stochastic simulation of a biological system, we use time regression models to describe the evolution in time of the concentration of a species with respect to the others.

The estimation of the noise (gaussian in this approach) may show peculiar behaviours when integrated into the fitted model.

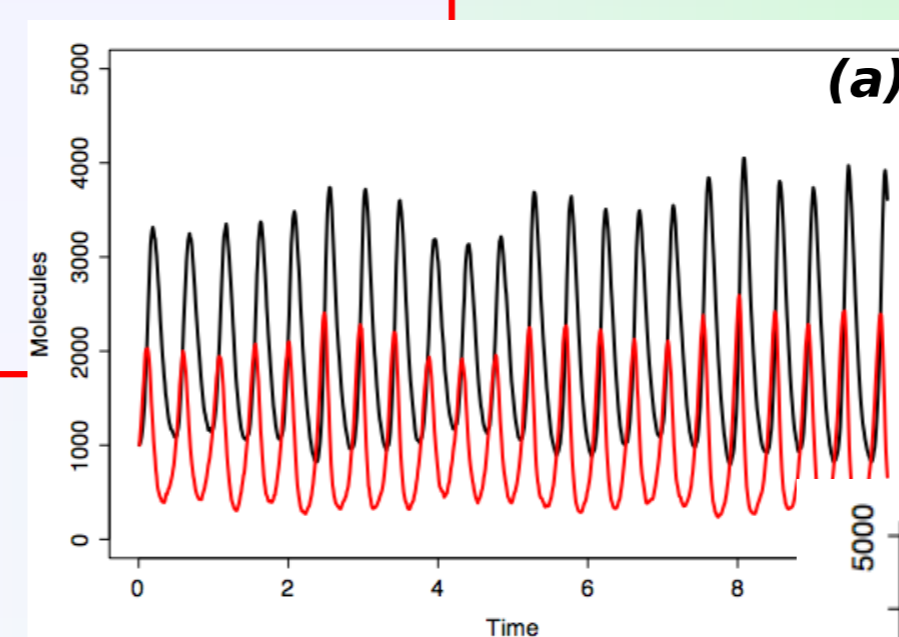
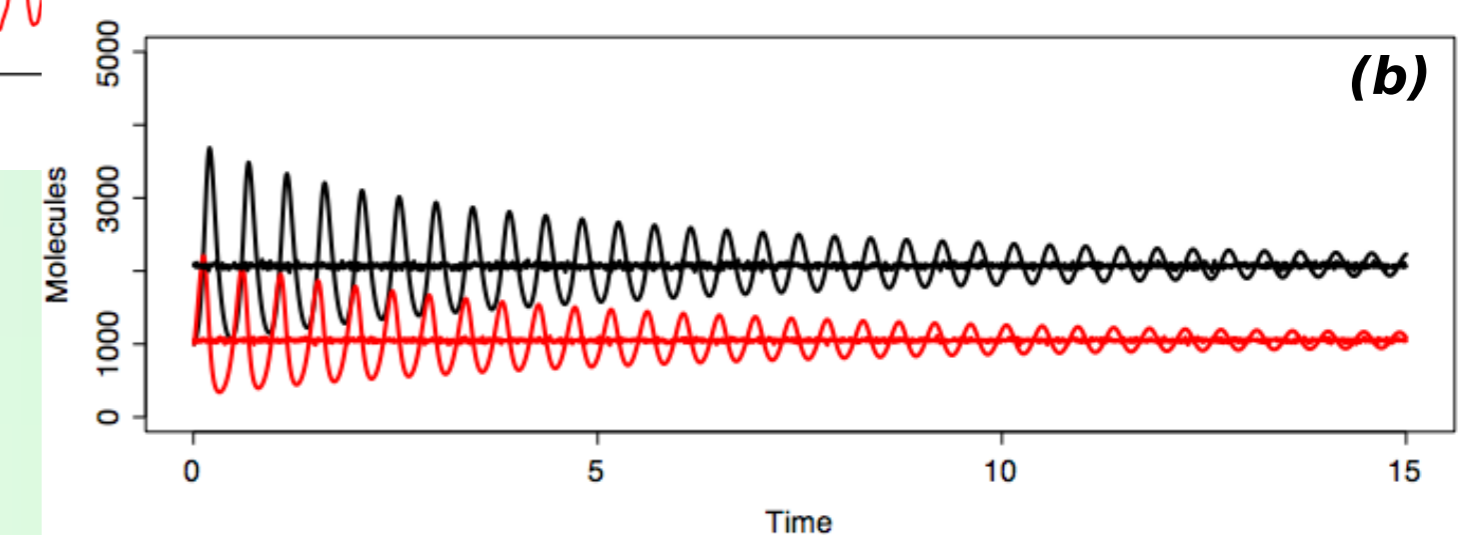
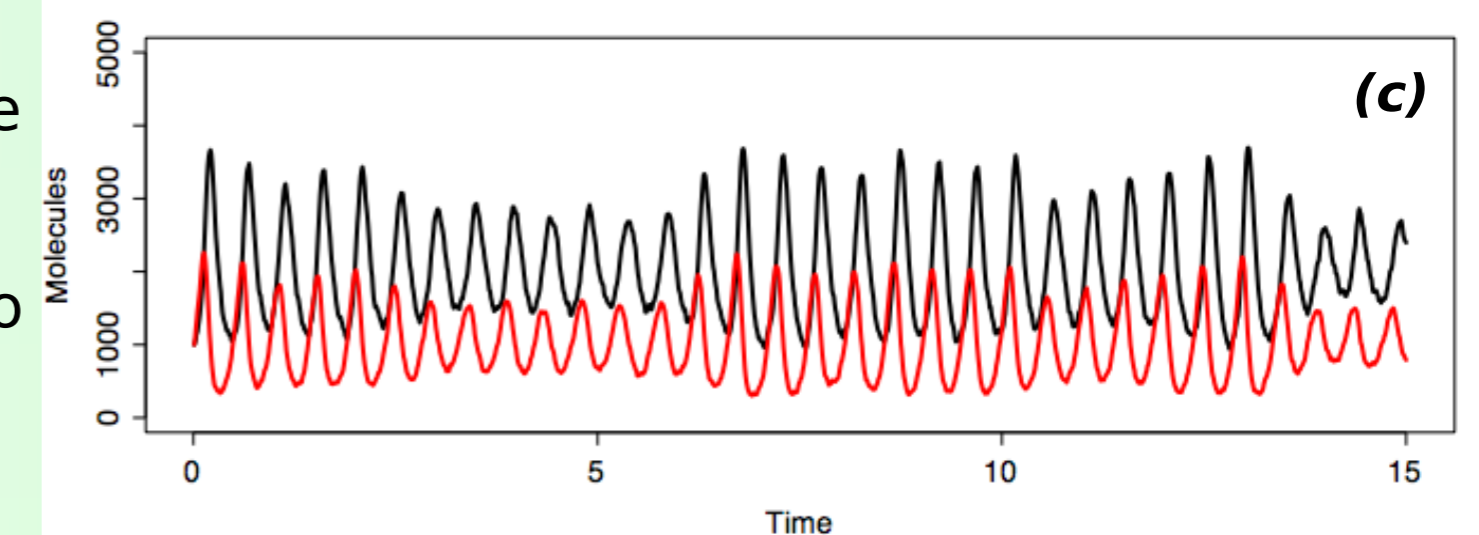


Figure 3. Statistical time regression models on oscillatory systems

A Lotka Volterra [3] stochastic simulation (a). Two predicted trajectories with the same initial point of the simulation (b) and (c).



The deterministic part of the model (b) predicts fading out oscillations, while, adding a simulated gaussian noise (represented in (b)) with mean and variance equal to the model residuals estimation, the system continues to oscillate (c).



Future work will concentrate on refining both the ICA approach and time regression models for a wide variety of cases and to finally automate these analysis as a support for biological noise investigations.

References

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