Parallel Session

Mathematical Methods in Biology VII

TRAVELING PULSES IN A TIME-DELAYED FITZHUGH-NAGUMO MODEL

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Keywords: Delay equations, Excitability, Traveling pulses, Fitzhugh-Nagumo.

Time delays can play an important role in biological and physical systems. A time delay can originate from signaling times, unknown intermediate processes, or other mechanisms. Mathematically, time delay can be introduced in a model by switching from ordinary differential equations (ODEs) to delay differential equations (DDEs). The inclusion of a time delay often leads to new and surprising behavior. In this work, we study the effect of a time delay in the Fitzhugh-Nagumo model. Although this model was originally developed to study the action potential in neurons, it has since become the prototypical model used to study excitability. We consider a piecewise-linear version of the Fitzhugh-Nagumo equations and study how the addition of a time delay changes the behavior of traveling pulses. We investigate analytically the dependence of the speed of the pulse on the model parameters and compare our analytical work with numerical simulation. Additionally we show how the results can be obtained approximately using perturbation theory. We find that the inclusion of a time delay slows down the pulses and, if large enough, can suppress pulses completely.

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DETERMINING THE MINIMAL OUTPUT SETS THAT ENSURE THE STRUCTURAL IDENTIFIABILITY OF A MODEL

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Keywords: Minimal output sets, Structural identifiability, Experimental design.

The process of inferring parameter values from experimental data may be a cumbersome task. In addition, the collection of experimental data may be time consuming and costly. This talk covers both these issues by addressing a fundamental scientific question: "Which experimental outputs should be measured to ensure that unique model parameters can be calculated?". Stated formally, we will discuss the topic of minimal output sets that guarantee a model's structural identifiability. A minimal output set can be defined as: *A minimal set of model outputs that needs to be measured to ensure that the model is structurally identifiable.* Due to its complexity and the associated computational demand, this topic has received very little attention and most scientists rely on intuitive experimental design. However, this may result in redundant experimental measurements. In this talk we present an algorithm tasked with identifying a model's minimal output sets. It is based on the numerical analysis (singular value decomposition) of a sensitivity based matrix. The elements of this matrix comprise of the sensitivities of the different model outputs to individual parameters over a certain time period [1]. Given the computational efficiency of this numerical analysis, it allows for the identification of all correlations between different model parameters via an iterative procedure. Minimal output sets are subsequently constructed by including model states that destroy these different correlations. A particular model may have multiple minimal output sets. This offers great flexibility to the experimental researcher as he/she can decide which set to measure taking factors such as time, cost and physical constraints into account. The present algorithm offers the opportunity to detect the full set of all possible minimal output sets. The algorithm will be showcased using 2 models: 1) a JAK-STAT model with 31 states and 51 model parameters that has 2 minimal output sets and 2) a smaller chemical reaction model that has 11 states and 6 model parameters. This model has 6 different minimal output sets [2, 3].

References

[1] Stigter JD, Molenaar J. (2015) *A fast algorithm to assess local structural identifiability*, Automatica, 58:pp118-pp124.

[2] Anguelova M, Karlsson J, Jirstrand M. (2013) *Minimal output sets for identifiability*, Math Biosci, 239(1):pp139–pp153.

[3] Liu, YY, Slotine JJ, Barabási AL. (2013) *Observability of complex systems*. Proc Natl Acad Sci USA, 110(7):pp2460-pp2465.

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NEW PERSPECTIVES AND PRACTICAL TOOLS FOR LOCAL IDENTIFIABILITY ANALYSIS OF BIOMATHEMATICAL MODELS

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Keywords: Ordinary differential equations, Local identifiability, Parameter estimation.

Biological system's dynamics is increasingly studied with nonlinear ordinary differential equations, whose parameters are estimated from input/output experimental data. Identifiability analysis aims at answering the central theoretical question whether the inverse problem is solved, uniquely, by a particular value of the free parameters, or if there are finite or infinite parameter vectors that produce identical input/output behaviour. Local identifiability is the intermediate situation with finite (often only few) multiple solutions that are necessarily isolated in the parameter domain. This leads to the ambiguous situation, in which multiple solutions imply identical model outputs but with different time courses of unmeasured variables, which are often a primary outcome of modelling studies. Parameters chosen randomly among equivalent ones, can lead to misinterpretations and to erroneous conclusions.

In this study we present the theoretical background for determining *all* parameter solutions of locally identifiable ODE models described by rational functions, showing that a comprehensive structural local identifiability analysis that includes *all* multiple solutions, reinforces the practical results. The adaptation of local identifiability analysis for practical purposes allows to calculate *all* the numerical solutions of locally identifiable models and the corresponding trajectories of unobservable states. The new approach appears applicable to moderately complex models.

In particular, the above theoretical results will be applied to a selection of representative examples taken from various research fields such as pharmacokinetics/dynamics, i.e. drug therapy; infectious diseases (e.g. HIV); uncontrolled cell proliferations (i.e. tumor growth).

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INFERENCE OF CAUSAL RELATIONS VIA DIMENSIONS

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Keywords: Causality, Takens' Theorem, Time delay embedding, Intrinsic dimension, Manifold.

Causality is one of the fundamental pillars of science. We presents a new method which is able to detect and quantify the probability of all types of causal relationships: independence, direct or circular causal connection as well as the existence of hidden common cause. The new method is based on the intrinsic dimension estimates of the joint and separate time delay embedding of the time series. We demonstrate the detection capabilities of our method on simulated examples and on different data series coming from in vitro, in vivo and human neuro-electrophysiological measurements as well as from economics. The method properly detected common cause during evoked activity of patient's EEG signals. During epileptic seizures the method reveals direct drive from the possible seizure onset zone and found common cause between the signals from the driven areas as well. The new method provides much clearer interpretation of interactions between recorded time series and promises applicability in many branches of science.

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ANTICIPATING NONLOCAL CRITICAL TRANSITIONS IN NEARLY-1D SYSTEMS

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Keywords: Early warning signals, Bifurcations, Chaos.

Much research in recent years has been devoted to the construction of generic methods for anticipating critical transitions from time series data. While a lot of progress has been made in this direction, there are shortcomings in the currently existing toolbox. At present, most indicators for critical transitions are only available for systems at equilibrium, whereas many systems in nature are inherently fluctuating. Time-series based indicators can also be difficult to interpret in real time: while it may be easy to see that a given indicator is rising, it is more difficult to infer how likely a transition is given such a rise, or to predict when it will occur. From the point of view of decision making in the prevention of critical transitions, such information is vital, and to provide this we may need to go beyond purely generic methods, and consider certain more or less specific properties of systems.

In this talk, I'll present a method for anticipating critical transitions in systems for which large parts of the dynamics can be reconstructed using 1D maps—a common property of systems in biology and ecology known as nearly-one-dimensionality. Using this property, we can predict nonlocal bifurcations of limit cycles and boundary crises of strange attractors, as well as more widely studied transitions such as saddle-node bifurcations. The method has the further advantage that it gives concrete predictions for the time of a transition, as well as the expected resilience of the system in the run-up.

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USE OF FIBONACCI NUMBERS IN LIPIDOMICS - ENUMERATING VARIOUS CLASSES OF FATTY ACIDS

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Keywords: Eliphatic amino acids, Fatty acids, Fibonacci numbers, Golden Ratio.

In lipid biochemistry, a fundamental question is how the potential number of fatty acids increases with their chain length. Here, we show that it grows according to the famous Fibonacci numbers when cis/trans isomerism is neglected [1]. For example, the number of unmodified fatty acids with 18 carbon atoms is given by the Fibonacci number 2,584. These include stearic acid, oleic acid and its trans-isomer elaidic acid, linoleic acid, vaccenic acid and the various isomers of conjugated linoleic acid. Since the ratio of two consecutive Fibonacci numbers tends to the Golden section, 1.618 . . . , organisms can increase fatty acid variability approximately by that factor per carbon atom invested. Moreover, we show that, under consideration of cis/trans isomerism, modification by hydroxy and/or oxo groups, triple bonds or adjacent double bonds, diversity can be described by generalized Fibonacci numbers (e.g. Pell numbers or hitherto scarcely studied number series). We build the proof on the recursive definitions of these number series [1].

Similar calculations can be applied to (proteinogenic and non-proteinogenic) aliphatic amino acids [2]. For that substance class, we allowed for single, double and triple bonds. An example of a non-proteinogenic amino acid involving a double bond and a triple bond is 2-amino-hept-4-en-6-ynoic acid produced by the basidiomycete *Amanita pseudoporphyria* [3]. Our results should be of interest for mass spectrometry, combinatorial chemistry, synthetic biology, patent applications, use of fatty acids as biomarkers and the theory of evolution. By considering the relative number of hydroxy and oxo groups as a proxy for hydrophilicity, the fraction of fatty acids or amino acids with certain properties can be estimated.

References

[1] S. Schuster, M. Fichtner, S. Sasso. (2017). *Use of Fibonacci numbers in lipidomics - Enumerating various classes of fatty acids*, Sci. Rep. 7 , 39821.

[2] M. Fichtner, K. Voigt, S. Schuster. (2017). *The tip and hidden part of the iceberg: Proteinogenic and non-proteinogenic aliphatic amino acids*, Biochim. Biophys. Acta – Gen. Subj. 1861 , 3258-3269.

[3] S.I. Hatanaka, Y. Niimura, K. Takishima. (1985). *Biochemical studies of nitrogen compounds in fungi. 22. Non-protein amino-acids of unsaturated norleucine-type in Amanita pseudoporphyria*, Trans. Mycol. Soc. Japan 26 , 61–68.