Parallel Session

Mathematical Methods in Biology IX

A NONPARAMETRIC ESTIMATION METHOD FOR SDE MODELS: AN APPLICATION TO CATTLE GROWTH

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Keywords: Stochastic differential equations, Individual growth, Nonparametric estimation, Cattle data.

We study stochastic differential equation (SDE) growth models to describe individual growth in random environments. The methods were applied to data on growth of the individual weight of bovines.

Usually in literature, nonparametric estimation methods for SDE are illustrated using financial data. In this area it is common to have data with observations at equidistant instants. This does not happen in our cattle weight data but the results can be derived for non-equidistant data. Also, the nonparametric estimators were developed for data from a single trajectory with abundant observations typical of financial data. Since, in our data, we have several trajectories available, with relatively few observations each, we needed to adapt the estimators [2].

Considering the diffusion process Y_t characterized by the autonomous stochastic differential equation $dY_t = a(Y_t)dt + b(Y_t)dW_t$, where W_t is the Wiener process, we estimate the drift coefficient $a(y)$ and the diffusion coefficient $b^2(y)$ using a nonparametric estimation method. The drift coefficient, also called infinitesimal mean, is the mean speed of growth of Y_t and the diffusion coefficient, also called infinitesimal variance, gives a measure of the local magnitude of the fluctuations.
Our goal was to assess if the parametric models (with specific functional forms for the drift and the diffusion coefficients) previously used by us to describe the evolution of bovine weight were adequate choices, or whether some alternative specific parameterized functional forms of these coefficients might be suggested for further parametric analysis of the data.

Nonparametric methods were useful to empirically validate our choices of parametric models, allowing us to take advantage of the parametric models to consider issues that are very hard to tackle with nonparametric methods, like estimate parameters, make predictions of future sizes, determine relevant indicators like the distribution of the time required for an animal to reach a prescribed market size, or even optimize the mean profit obtained by raising and selling an animal and compute the probabilities involving the selling profit [1].

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ON THE FEASIBILITY OF COMPLEX SYNTHETIC BIOLOGICAL CIRCUITS

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Keywords: Synthetic biology, Distributed computation, Wiring problem, Stationary phase.

The implementation of a biological computer has been one of the most remarkable challenges in the field of biotechnology in the last few decades. All kinds of logic gates have been developed to work in bacteria and eukaryotes. This has allowed to design several circuits with minimal complexity. However, soon it was evident that an arbitrary complex circuit requires the distribution of its components among different types of cells that communicate between them. This communication is what we call a wire. So far, we know that a circuit implementation without spatial segregation would be virtually impossible if the numbers of wires is too high, so now the scientific community is moving towards the spatial segregation of the circuit. Nevertheless, not so much effort has being paid to solving the wiring problem, and to measuring the actual limitations of the wires themselves. Here we show a very simple model for non-growing cells connected through a wire that is able to predict the behaviour of the system. We also explore the logic capabilities of a wire and show that these capabilities are compatible with the wire acting as a buffer. Finally, we show that a system of several cell types connected through wires can work as intended if and only if an algebraic system of conditions in the form of linear inequalities is obeyed. In summary, the feasibility of a complex biological circuit is equivalent to the solution of a linear programming problem.

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3D GEOMETRICAL MODELS OF LIVER TISSUE UNCOVER UNKNOWN FEATURES OF NON-ALCOHOLIC FATTY LIVER DISEASE

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Keywords: 3D geometrical models, Tissue reconstruction, Disease progression.

The liver is a vital organ that executes numerous functions such as storage of nutrients, detoxification, metabolism and protein synthesis. It acts as link between the digestive and circulatory systems of the body through two networks, the bile canalicular (BC), where the bile is secreted and flows, and the sinusoidal endothelial network, which carries the blood to hepatocytes throughout the parenchyma. The hepatocytes constitute $\sim 80\%$ of the liver volume. Together with sinusoidal endothelial cells, stellate and Kupffer cells they give rise to a complex three-dimensional (3D) tissue architecture. The BC and sinusoidal networks have an intrinsic 3D topology and therefore, their structure cannot be properly described by two dimensional (2D) approaches. Yet, 2D histology is the current gold standard to diagnose several liver diseases (e.g. non-alcoholic Fatty Liver Disease (NAFLD)). The absence of 3D information results in an incomplete understanding of both liver physiology and physiopathology. Reconstructions of digital models of tissue with sub-cellular resolution from microscopy images (i.e. 3D geometrical models) constitute a powerful tool for understanding tissue structure in 3D and uncover morphological changes occurring in the tissue during diseases progression. In this study, we reconstructed 3D sections of liver tissue from healthy individuals and patients with NAFLD at different stages of disease progression. First, human liver sections obtained by biopsy ($\sim 100\mu m$ thick) were optically cleared, stained for e.g. cell border, BC network, sinusoids, lipid droplets and nuclei, and imaged using multiphoton microscopy. Second, the main components of liver tissue architecture were reconstructed using our open-source software 'Motion Tracking' [1]. We reconstructed different cellular and sub-cellular structures, including central and portal veins, bile canaliculi, sinusoids, nuclei, hepatocytes and lipid droplets. Finally, we performed a quantitative morphometric and spatial analysis of the different tissue components during different stages of NAFLD.

The resulting geometrical models provided a complete description of different morphological parameters across multiple scales, from tissue to sub-cellular level, and uncovered a

significant amount of new information about morphological changes occurring in NAFLD. Preliminary data show that morphological properties of the BC network (diameter, connectivity and ramifications) in steatotic liver tissue are correlated with a porto-central gradient of lipid droplets agglomeration in hepatocytes. Further work will focus on identifying statistically relevant bio-markers (e.g. hepatocyte ploidy levels, zonated lipid droplets agglomeration, etc.) for the early detection of disease in human liver samples in NAFLD and insights into its pathogenic mechanism.

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A 3D MATHEMATICAL MODEL OF CENTIPEDE LOCOMOTION ON ROUGH TERRAIN

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Keywords: Mathematical model, Experimental observation, Locomotion, Centipede.

We study locomotion change of a centipede which moves on ground with various geometries. A centipede has more than 40 legs and it can move quickly in many natural environments. It is obviou s that it uses not only a centralized control for legs but also an autonomous decentralized control, however, none of the control rules is known yet.

To understand the control rules, we focus on the centipede *Scolopendra subspinipes mutilans* which takes on the locomotion style "retrograde wave" in which the density wave of legs propagates in opposite direction to the motion of the centipede [1] and it uses a body undulation when it moves with high velocity. We put the centipede on a long and narrow lane which is made of styrofoam. The lane undulates in a sinusoidal manner and the wave length and the amplitude is the same as the length of a few body segments. At a low velocity of about 20mm/s, the centipede searches the geometry of the ground surface by using its antenna and puts its front legs on the top of the hills. After the front legs are put onto the tops, the next legs follow. As a result, all legs touch the same points i.e. the top of the sinusoidal wave, and thus the retrograde wave is observed. On a flat lane, phases of the density waves of legs on the right and left side are always anti-phase. On an undulating lane, both anti-phase and in-phase waves are observed when the wave length of the undulation is about a few body segments length. As the wave length of undulation increases to about 6 body segments length, only in-phase density waves emerges.

At a high velocity of about 100mm/s, like in an emergency situation, the centipede does not care to put his legs onto the tops of the sinusoidal ground anymore, and it uses a body undulation instead. Centipedes without antenna hesitate to move on the sinusoidal lane.

Based on these observations, we propose a three dimensional mathematical model with a centralized control by using its antenna and an autonomous decentralized control using the feedback information from legs. It was reported that such an autonomous decentralized control leads to the retrograde wave on a flat ground in two-dimensional simulations [2, 3], in which right and left legs were not distinguishable. We perform numerical simulations of

our centipede model on rough ground and we present a similar transition from the anti-phase to the in-phase mode by changing the wave length of the sinusoidal wave of the ground. We also discuss the efficiency of the locomotion with/without undulation on flat and rough ground.

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WEIGHTED ENSEMBLE SIMULATIONS OF BIOMOLECULES

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Keywords: Weighted ensemble, Molecular dynamics simulation, Dynamical Systems, Biomolecules.

Weighted ensemble (WE) method is an efficient way to numerically sample nonequilibrium trajectories generated by random dynamical systems such as described by Langevin dynamics. It was introduced by Huber and Kim [1] for Brownian dynamics of biomolecules and has been further extended by Zuckerman and coworkers for general dynamical systems [2]. Our main focus here is to apply this method to biomolecules such as proteins and peptides and to discuss how to extract kinetic information and the features of nonequilibrium trajectory ensembles.

In the WE method, one first has to prepare a "state space" constructed by several collective variables or order parameters. Dividing such state space into several pieces called "cells", we execute, for example, molecular dynamics simulations in each cell. We can run the simulation in parallel and each trajectory in a cell has a weight, from which we can recover the density information in each cell. In a conventional implementation of the WE method, the number of trajectories in each cell is fixed, however, a trajectory can cross the cell boundary, resulting in the increase or decrease of the trajectory number in a cell. We thus make use of a death-birth procedure for a trajectory and reduce or increase the number of trajectories up to the fixed number. At the same time, the trajectory weight should be changed because the density in each cell should not be changed. This is the basic procedure of the WE method for describing nonequilibrium dynamics.

We apply this WE method to several biomoleculear systems. The first example is an artificial peptide called chignolin, which only has 10 amino acids but is known to have at least two stable states, a folded and misfolded states. The free energy landscape has been previously characterized by using enhanced sampling techniques [3] and the relaxation mode analysis

[4], but its kinetic properties still need to be elucidated. We used the previous MD simulation data at high temperature (420K) in [4] and applied the non-Markov type analysis [5] and milestoning type analysis [6] to extract kinetic properties [7]. However, it is not feasible to carry out such analysis at room temperature because the process becomes slower, and this is a typical problem when we are concerned with larger systems with slower timescales. Here we apply the WE method to this type of slow process, and calculate the kinetic properties of chignolin at the room temperature as well as at the high temperature [8]. Furthermore, we also apply the WE method to other slower processes such as a local proline isomerization of PIN1 enzyme and the global conformational change of adenylate kinase.

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