Physics of behavior across scales

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SUMMARY

Animal movement is remarkably rich, spanning multiple spatiotemporal scales and exhibiting an intricate combination of variability and sterotypy. We have no trouble identifying movement patterns, such as walking or jumping, even though the precise body motion can be quite variable, with each repetition being slightly different from the last. Similarly, longer time scale sequences of behaviors may appear random, but generally fit higher order interpretable patterns or goals. It is therefore essential to find succinct representations that characterize movement dynamics on multiple scales, if we hope to make connections between motile behavior and the underlying neural, genetic and environmental control mechanisms.

In this thesis, we explore novel physics approaches to the understanding of animal movement. In particular, we focus on the undulatory motion of *C. elegans*, a tiny worm (~ 1 mm) with a small, fully mapped, nervous system (~ 300 neurons). Worms move by propagating sinusoidal waves along their body and their behavior is typically composed of sequences of forward movements interrupted by sudden reversals and turns, in which the worm coils into itself to change the direction of locomotion. Despite its apparent simplicity, this organism is capable of remarkable behavior, orchestrating a large number of degrees of freedom in order to find food, mates, and adapt to changes in the environment. In addition, decades of research on the biology of the worm provide a deep understanding of its brain, its genes, and the way it develops from an egg to a fully developed organism. Guided by this deep level of biological understanding, we will use *C. elegans* as a test-bed for new quantitative approaches to behavioral analysis, revealing novel insights into the fundamental principles underlying movement behavior.

In **Chapter 2**, we study *C. elegans* motility from a coarse-grained perspective, treating the worm as a vector in the two-dimensional plane, defined from the centroid to the head of the worm. We take video recordings of worms freely moving on an agar plate, and study the trajectories traced by them over time using three measurements: the speed, the angular bearing

with respect to the lab frame, and the orientation of the movement (forward vs backward). Observation indicates that the movement is rather unpredictable, and therefore capturing its essential features requires a statistical description, analogous to that of the Brownian motion of a particle suspended in a fluid. We thus build a succinct parameterization of the dynamics through simple stochastic models built independently for the speed, bearing and orientation dynamics. The speed is modelled through a noisy forcing that relaxes to a mean value on a characteristic time scale. The bearing dynamics are parameterized as a diffusion process with a linear drift, which captures fluctuations about an overall trend. Finally, the orientation dynamics are modelled as a discrete jump process characterized by the time scales of forward and reverse runs. In total, the model is comprised of only 7 parameters: three for speed, two for bearing and two for orientation dynamics. Despite its simplicity, this model accurately captures the statistical properties of the dynamics, and simulations yield trajectories that are remarkably similar to those performed by worms.

C. elegans is part of the *Nematoda* phylum, one the largest and most diverse groups of species. Despite the large variety of habitats in which these nematodes can be found, they share a remarkable degree of anatomical similarity. This allows us to apply the same model across species and therefore study behavioral variability through the variation in the model parameters. We successfully applied our modelling approach to the trajectories of a dozen worms from nine different species of nematodes. Studying the model parameters across worms reveals a main mode of variation which captures a trade-off between exploration and exploitation: on the one end we have worms that exhibit slow speeds and large number of transitions between forward and backward movements (exploiting a local region), and on the other end we have worms that move in relatively straight paths at larger speeds (exploring larger areas). Using this main mode of variation as a phenotype, we find that while some species exhibit a large specificity to their behavior, most exhibit within-species variation that is comparable to that of the across species variability. These differences suggest a possible bet-hedging mechanism, in which individual-to-individual differences are increased in order to provide the species with an evolutionary advantage to deal with variable environments.

In **Chapter 3**, we zoom further into worm behavior and study fine scale changes in body posture. We take measurements of worms freely moving on an agar plate, and extract the body's centerline from high resolution video tracking. We use a dimensionality reduction technique, called Principal Component Analysis (PCA), to extract a set of lower dimensional modes (called "eigenworms") that captures the wide variety of distinct body postures worms can perform. The time series of "eigenworm" projections provides a way to study the dynamics of the body posture. Close inspection reveals that fine scale postural dynamics is extremely complex, with every single body wave being different from the last. Our approach to the modelling of these dynamics is to decompose them into shorter segments, within which the time evolution of the body posture could be well approximated by linear dynamics. The idea is that even complex dynamics may be locally linear, in the same way a complex shaped surface is locally flat. Linear dynamics are simple: trajectories can only grow, decay, or oscillate. Nonetheless, by tiling together a collection of linear dynamical systems with parameters that change time, we can neatly reproduce complex dynamical patterns in a variety of systems. We use a likelihood-based approach to identify where dynamical breaks occur: as we grow the size of the local window, we essentially ask how likely is it that the new time points can be predicted by the same set of linear parameters. Using this adaptive approach therefore slices a time series into a collection of window of different sizes, within which the dynamics is approximately linear. We leverage this parameterization to cluster the locally-linear dynamics using a novel likelihood-based dissimilarity metric. Applied to the worms dynamics, this method recapitulates the well-known stereotyped behavioral motifs (forward movement, reversals, and turns), but also reveals finer scale variation in these states, including new motifs previously overlooked by ethologists. Given its generality, we were able to apply this method to a large variety of complex time series, revealing interesting structure in the neuronal dynamics of *C. elegans*, mice and local field potential recordings in Monkeys.

Interestingly, we find that across systems the linear dynamics fluctuates in the boundary between stability and instability, in a dynamically critical state that provides the system with a large degree of susceptibility to external stimuli, and that can be modulated either internally or through external perturbations. Transitions between forward and backward locomotion in the worm are accompanied by a bifurcation in the local dynamics from stable to unstable states. Similarly, we find that lower awareness states in the brain of the worm (quiescence) or the Monkey (anaesthesia) induce a shift in the stability of the linear dynamics towards more stable states, therefore lowering the systems susceptibility to external perturbations. These subtle changes in stability can be advantageous by providing the system with a larger degree of flexibility and maneuverability.

In **Chapter 4**, we introduce a novel framework to understand how long time scale exploration strategies (Chapter 2) emerge from combinations of fine scale posture primitives of behavior (Chapter 3). This chapter serves as a theoretical introduction to the following chapter, in which these ideas are applied to the worm locomotion. In systems with a very large number of degrees of freedom and complex non-linear dynamics, the knowledge of the equations of motion often provides little understanding over the phenomenological properties of the system. Take a gas, for example: in principle, we could follow the position and velocity of all the molecules, which sum up to order $O(10^{23})$, and try to write down the equations of motion. However, that would not necessarily allows us to understand the ensemble properties of the gas, such as its temperature, pressure or volume. We will therefore attempt to abstract from the fine-scale trajectory based approach, and study instead the time evolution of ensembles in state space. One of the advantages of the ensemble-based approach is that we can write down a single linear operator, the Perron-Frobenius operator, that evolves densities in time. We essentially trade a finite set of non-linear equations of motion, by an infinite-dimensional linear operator, which we can approximate by making small partitions in the state space and estimating the transition probabilities between these discrete states. We can then use this transition matrix to decompose the dynamics into a hierarchy of spatiotemporal modes and find regions of state space that remain coherent for a long time.

In order to do this from measurement data, we first need to reconstruct the state space of the dynamical system, i.e., to find the set of variables that evolves according to a first order differential equation, meaning that we can predict the immediate future state using only the current state. As an example, take the motion of a bead attached to a spring. Newtonian mechanics dictates that the bead's acceleration is proportional to the position with respect to the rest state, with the proportionality constant given by the spring constant and the mass of the bead. The acceleration is defined as the second order derivative of the position: it measures how the velocity changes, which is a measure of how the position changes. What this means is that position alone will not be enough to specify the immediate future of the bead. In fact, we need to know not only the position, but also the velocity in order to know whether the bead is moving away or towards the rest state of the spring. Another way to make an accurate prediction of the future state is to look at the position of the bead at time $x(t)$ and at a time delay $x(t-\tau)$. Adding this extra dynamical degree of freedom into the definition of state yields a maximally predictive state that evolves according to a first order differential equation. In physics, we call this the phase space or the state space of the dynamics. Working with the state space unleashes a higher degree of analytical power, as well as access to dynamical invariants, symmetries and conservation laws. In addition, the ensemble-based approach relies on the fact that we can estimate densities in the full state space. Therefore, we need to reconstruct the state space in order to be able to extract the long-lived patterns of the dynamics from measurement data. In this chapter, we introduce a novel approach to state space reconstruction that leverages the approximation of the Perron-Frobenius (PF) operator to find a maximally predictive state space. We add time delays into the measurement time series and estimate how unpredictable the dynamics is by measuring the entropy rate of the associated PF operator. Without enough delays, the system will look more unpredictable and therefore the entropy rate will be high. As we increase the number of delays, the entropy rate starts decreasing, slower and slower as we approach the right number of delays at which the entropy rate stops changing. This allows us to find the optimal amount of time delays for reconstructing the state space, and also yields a state space discretization which enable an approximation of the PF operator that accurately captures the long time behavior of the system. We then study the spectrum of the operator and extract coherent sets by clustering the first non-trivial eigenfunction, which is the one that decays the slowest to the invariant density. This effectively splits the state space into regions that remain coherent with the flow, meaning that they transition more within that region than outside of it.

To illustrate the extraction of long lived states, we apply this method to the dynamics of an overdamped particle in a double well potential driven by thermal noise. In this case, the slow behavior of the system corresponds to the hopping between the potential wells, which can be neatly identified by clustering the slowest eigenfunction of the PF operator. We demonstrate our state space reconstruction framework with an application to the Lorenz system in the standard chaotic regime. We take incomplete measurements, the time series of the x variable, and try to reconstruct the full state space and its ergodic properties. As we add delays, the entropy rate decays until it stops changing, at which point we have reconstructed the attractor. The topology of the reconstructed trajectories matches that of the underlying dynamical system, and we recover the entropy rate. In addition, we also recapitulate the long time scale spectrum of the PF operator, which remarkably enables us to identify the almost invariant sets of the Lorenz system from incomplete time series measurements. Finally, we make a bridge between deterministic and stochastic dynamical systems by coupling a particle in a double well with the y variable of a fast Lorenz system in the chaotic regime. We use our approach to reconstruct the state space of the dynamics, and recover the underlying time scale separation of the system as well as identify that the slowest dynamics correspond to the hopping between potential wells.

In **Chapter 5**, we apply these ideas to the posture dynamics of *C. elegans*, in order to extract long lived behavioral states from fine scale posture measurements. We start by analysing time series of lab strain N2 worms freely moving in a featureless environment. After extraction of the centerline, we again project the data into the lower dimensional "eigenworm" space. The first step in the analysis is to reconstruct the state space by adding time delays and studying the evolution of the entropy rate of the associated Perron-Frobenius operator. Using this approach, we find that $K^* = 10$ frames is enough to unfold the posture state. We then partition the reconstructed state space and study the spectrum of the associated transition matrix. The slowest eigenfunction decays to the equilibrium distribution on a time scale of ~ 10 s and clustering it reveals long time scale behavioral patterns of forward locomotion and pirouettes: composite behaviors in which the worm performs a reversal followed by a ventral turn. The duration of pirouettes is of order $O(10)$ s, while forward bouts can be as long as $O(100)$ s, much longer than the measurement time scale of $O(0.1)$ s. Using a similar approach, we can further decompose the dynamics into finer scale behaviors, which evolve over shorter time scales: we find that ventral turns generally occur after reversals, while dorsal turns generally occur during forward locomotion. We further show that we can use the Perron-Frobenius operator to simulate fine scale posture time series, recovering both the stationary properties of the dynamics as well as the time scales of transitions between coarse-grained states.

In the previous analysis, N2 worms were on an environment without food in which they mostly move at higher speeds and explore a large portion of the plate. In contrast, when on food, worms exhibit much longer time scale behavioral patterns, transitioning between a roaming state, characterized by higher centroid speeds and lower angular speeds, and a dwelling state, in which worms stay in a local region of the plate and move at lower speed and higher angular speeds. Switching between these unobserved internal states is driven by changes in the expression of different types of neuromodulators, that effectively change the frequency with which worms transitions between different fine scale behaviors. For on-food worms, the entropy rate as a function of the number of delays indicates that $K^* = 15$ frames is enough the reconstruct the state space, which we partition in order to build an approximation of the PF operator. Analysis of the spectrum shows that the slowest decaying eigenfunction takes about $O(100)$ s to decay to the invariant density, about an order of magnitude longer than the decay time obtained in the off-food setting. Notably, clustering this eigenfunction yields two coarse-grained states with dwell times of up to ~ 500 s, which we can show correspond to the previously described roaming and dwelling states. We can therefore extract changes at the level of neuromodulation on long time scales, from high resolution posture measurements on short time scales.

Given the tremendous effect food has on the behavior of N2 worms, we decided to study a genetic mutant with a modified response to food: *npr-1*. The *npr-1* mutations impairs the expression of a neuropeptide receptor in a collection of sensory neurons, which would serve to inhibit their sensitivity when the conditions are favorable. In the absence of this receptor, *npr-1* worms become hypersensitive to the effects of environmental oxygen and pheromones. Because of this, the *npr-1* mutation overrides the transition from roaming to dwelling, and these worms typically move at higher speeds than N2 worms on food. As before, we take high resolution posture measurements of *npr-1* mutants crawling on a food-full plate, and study the time series of the lower dimensional projection into "eigenworm" space. Using the behavior of the entropy rate as a function of the time delays, we choose $K^* = 11$ frames to reconstruct the state space, which we then partition in order to approximate the action of the PF operator. Unlike the N2 behavior on food, the longest time scale of the operator is now of $O(10)$ s, similar to what we found in the N2 off-food behavior. Therefore, we find a mutation that effectively removes the long time scale behavior found in wild type N2 worms on food.

The decomposition offered by the PF operator provides means to build effective phenomenological models on the slow dynamics. In fact, in ergodic systems with a large time scale separation it is possible to identify effective hydrodynamics variables, which are driven by noisy terms that correspond to the fast dynamics. Inspired by these approaches, we decided to study the time evolution of the projection onto the slowest eigenfunction of the Perron-Frobenius operator. As a first order measure of the dynamics, we computed the autocorrelation function of the slowest non-trivial eigenfunction across experiments. Remarkably, the slow dynamics of N2 worms exhibits long range correlations of $O(100)$ s. In addition, the *npr-1* mutation destroys these long range correlations, decaying in ~ 10 s. Plotting the N2 autocorrelation functions in a log-log scale, we find a significant power law regime, with an exponent that is higher off food (indicating the correlations decay slower on food). Power law autocorrelation functions are found in systems with scale free correlations and therefore we decided to take a renormalization group approach in time: we average the eigenfunction projections in short windows and re-estimate the autocorrelation functions. Remarkably, the autocorrelation functions collapse after rescaling according to the correlation time, providing further strong evidence of the scale-free nature of the dynamics. Power law behavior in the dynamics of hydrodynamics variables is a signature of out-of-equilibrium systems with conservation laws. The fact that *npr-1* does not exhibit long range correlations indicates that this mutants fail to maintain the conservation law. Interestingly, this is consistent with physiological studies that show that the NPR-1 receptor is essential to keep the balance between excitation and inhibition in motor neurons and to maintain homeostasis. These results suggest that slow hydrodynamic modes with scale-free correlations might exist due to the fact that organisms have evolved to orchestrate a large number of degrees of freedom, while keeping a tight balance between order and disorder.

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