

Landscape of Target State Directed Processes in Living Systems

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Across the living world, from cell biology and morphogenesis to behavior and cognition, system dynamics is often directed towards functionally important goals one might call target states. Dynamics towards such target states is never in equilibrium, always nonstationary, and typically swiftly over, terminating once the goal is reached. Complicating data-driven inference of effective dynamical models, trajectories of living systems homing in on target states are not only brief but exhibit initial conditions that are typically intrinsically heterogeneous and experimentally uncontrollable. Here we present a reverse-time stochastic dynamics theory for ensembles of target state directed processes, and uncover a universal space-time core of such ensembles that is independent of initial conditions. Examining this core structure, we demonstrate that the landscape of conceivable target state directed dynamics decomposes into sectors that qualitatively differ in their accessibility to data-driven inference. Ensembles undergo a phase transition from an opaque phase, in which their space-time core is uninformative about the underlying dynamics, to a transparent phase, in which the dynamics is directly encoded in its low-order moment functions. We use the reverse-time theory of target state directed processes to construct core-based methods for data-driven dynamical systems inference. Applied to biophysical models of cytokinesis, a directed process for which different regimes of actomyosin turnover cause distinct types of terminal dynamics, our approach precisely identifies the underlying molecular mechanism. Reverse-time ensemble theory establishes a versatile toolset for understanding target state directed biological processes and reveals that the mere presence of target states in living systems induces a novel kind of phase transition in dynamical systems inference.

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I. INTRODUCTION

The dynamics of living systems is often directed towards functionally important target states. Prominent examples of such target states (TSs) are transition states in the cell cycle such as cell separation in cytokinesis or cell cycle checkpoints [1–7], branch-points in cell fate determination [8–13], or discrete behavioral decisions generated from the continuous accumulation of sensory evidence [14,15–19] (Fig. 1). Target-state-directed dynamics are crucial for the functioning of biological systems on various scales, and considerable effort has been dedicated to clarify their phenomenology and mechanistic underpinnings [3,11,18,20]. In many instances,

target states are not approached deterministically [7,13,14]. Rather, due to internal and external sources of fluctuations, biological systems typically generate a diverse set of trajectories all homing in on the same target state, and thus they require an ensemble treatment.

The terminating nature of the target state approach raises general questions about the identifiability of such dynamics from experimental time-series observations. Because the action of a target state-directed dynamics is restricted to short snippets of time, the most rapid mechanisms may potentially leave the weakest signatures in time-series recordings. In addition, on short timescales, a stochastic dynamics becomes increasingly indistinguishable from undirected Brownian motion. Specifically in living systems and distinct from computational studies or biophysical *in vitro* experiments, experimentalists typically do not have sufficient control to impose initial conditions of the system state. Obviously, imposing uniform initial conditions would facilitate uncovering effective dynamical laws. This, however, is often impossible in systems such as dividing cells, animals solving decision-making tasks, or gene regulatory networks converging on a

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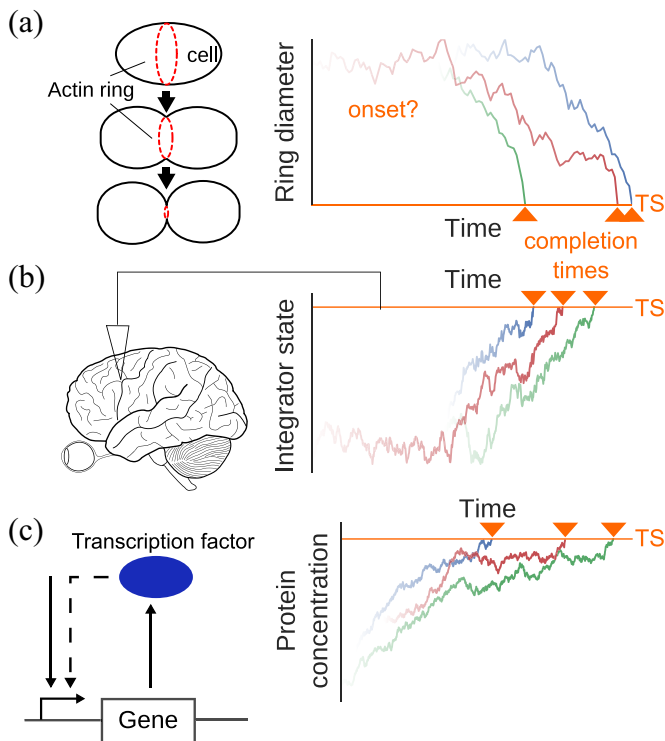


FIG. 1. TS-directed dynamics occurs across different levels of biological organization and function. Biological processes often achieve functional goals and hence feature clearly defined end states. Determining the precise onset of the action of directed dynamics in living systems is often impossible due to their transient activation. In addition, practical limitations typically preclude the experimental preparation of an initial state. (a) Cytokinesis converging towards cell separation (cell biology). (b) Neuronal evidence accumulation converging towards a decision threshold (cognitive neuroscience). (c) Gene regulatory network activation converging towards the stable expression of cell type regulators (gene regulation). Target states and completion times are marked. Notably, biophysical models of these processes fall into distinct regimes of stochastic terminal dynamics.

cell fate state. Even in computational settings, initial distributions can effectively be inaccessible [21]. A notable example is protein folding, which proceeds along a reaction coordinate toward a well-defined native structure, yet the unfolded initial ensemble is extremely broad [22,23]. In simulations of ligand-binding dynamics, used in medical compound discovery, only the bound pocket is clearly defined, while the unbound ensemble spans the entire dissolved state space [24,25]. This causes the acceptance rate of conventional path-sampling moves to plummet to near-zero, rendering simulations inefficient [26].

On top of this challenge, at process onset one cannot assume that the same dynamical laws are in action across an ensemble of observations: Living systems often transiently “activate” different types of dynamics by processes that are not easily observable, and thus “early” sections of trajectories exhibit additional sample-to-sample heterogeneity. The time of target state arrival, in contrast, is typically extremely well defined, and trajectories in its vicinity are most pure. For these reasons, aligning observed trajectories at the target state appears biologically and practically to be the superior choice. Intriguingly, however, the statistical dynamics of processes

in such a target state aligned representation including corresponding system identification techniques has never been theoretically examined, although target state alignment is a common practice in the calculation of descriptive statistics in fields from biophysics [27–29] to cognitive neuroscience [30].

With target-state alignment, time-to-completion is the natural temporal frame of reference for analyzing ensembles of measured trajectories or model sample paths. Because with increasing time to completion time advances in reverse, the reverse-time stochastic dynamics [31] appears as the appropriate mathematical starting point to dissect TSA ensembles. Used in nonequilibrium statistical mechanics [32,33] and rare event sampling [34], reverse-time stochastic dynamics recently gained prominence as a tool for constructing generative models by unsupervised learning that can sample from complex, multimodal data distributions [35,36]. Note that reverse-time stochastic dynamics is not to be confused with the Backward-Fokker-Planck formalism, which, despite the name, still describes dynamics in forward time [37].

Both generative diffusion models and the analysis of the target-state approach are based on dynamically evolving, out-of-equilibrium, statistically nonstationary ensembles. A qualitative comparison of the two settings indicates that using reverse-time stochastic dynamics in the analysis of the target-state approach must be expected to raise novel challenges. In generative diffusion models, a forward stochastic dynamics is designed to guarantee convergence of the evolving probability distribution from a complex initial distribution to a simple Gaussian equilibrium. Reverse-time stochastic dynamics is then used to generate samples from the complex out-of-equilibrium initial distribution by evolving states, drawn from the Gaussian equilibrium, backward in time. In a target state directed dynamics, no such asymptotic equilibrium distribution exists, rather during forward dynamics any set of initial conditions collapses into a singular distribution concentrated on the target state. This is more akin to an assembly of randomly kicked particles falling into a black hole than to a system relaxing to a state of thermal equilibrium.

What is inferred in diffusion models is not the forward dynamics but the form of reverse-time guiding forces that guarantee the recovery of the complex initial distribution by reverse-time evolution. Such guiding forces will also occur in a reverse-time representation of the target-state approach, but in this case they must take a radically different form. Here the reverse-time representation has to contain terms that explosively drive reverse-time paths away from the target state, a phenomenon that has no counterpart in generative diffusion models. In addition, during this reverse-time expulsion from the vicinity of the target state, sample paths need to be forced to disperse in a way that regenerates a finite entropy, intermediate distribution before this distribution can converge to the shape of the forward initial condition.

These distinctive features raise a range of fundamental questions: Is the form of this reverse-time repulsion system-specific and informative about the underlying dynamics, or does it take a system-independent form as trajectories in reverse time must be driven away from the target state irrespective of the forward laws of motion? Assuming that such system-independent forces exist, how can they be separated from whatever informative system-specific forces are present,

and how can the latter be used for dynamical systems inference? In addition, reverse-time guiding forces that ensure correct recovery of the forward initial distribution will in principle be present in the reverse-time dynamics at all times and thus also in the vicinity of the target state. Does the presence of these guiding forces then undermine our core hypothesis that during the target-state approach the ensemble becomes insensitive to initial state heterogeneity and fade-in effects and thus a purified, robust base for dynamical systems inference?

Starting from Anderson's theory [31], in the following we construct a novel reverse-time representation of TSA ensemble dynamics that resolves these questions. In particular, we show that a TSA reverse-time dynamics will in general decompose into two phases: a first phase during which reverse-time trajectories are repelled from the target state and dispersed relative to each other such that the entropy of the initial distribution is roughly restored, and a second phase representing convergence to the exact distribution of initial conditions. While the second phase is obviously sensitive to the distribution of initial conditions, we find that their impact on the first phase is exponentially suppressed. As a consequence, the density functional of a TSA ensemble exhibits a space-time core, representing the first phase, which forms a basis to infer target state-directed dynamics in a way that is shielded from variable and uncontrollable initial conditions and tune-in effects.

Below, we first revisit the diversity of potential terminal dynamics and explore the nature of TSA ensembles for a simple but instructive example. We then develop a general theory for ensembles in the target state approach using reverse-time stochastic dynamics. We demonstrate the existence of a universal space-time core of such ensembles that is independent of forward initial conditions. Examining this space-time core for a representative trans-section of model space uncovers a fundamental phase transition in the identifiability of TS-directed dynamics. We use this theory to derive core-based methods for data-driven dynamical systems inference. Applied to the dynamics of cytokinesis, we demonstrate that our approach successfully detects different regimes of actomyosin turnover from target state aligned time series.

II. TWO REGIMES OF STOCHASTIC TERMINAL DYNAMICS

Before we develop a general theory of TS-directed dynamics, we begin by examining a set of simple model problems that are of biological significance in a wide range of living systems and at the same time cover qualitatively distinct types of terminal dynamics. What form of target state directed dynamics is functionally most suitable will generally depend on system-specific factors. In many systems, however, it will be advantageous to reach a target state swiftly and robustly. Considered in a stochastic dynamics setting, there are two fundamentally different types of target state directed dynamics: those in which the target state arrival time stays finite in the deterministic, low-noise limit, and those with an arrival time diverging in this limit [Fig. 2(a)]. The latter applies if the target state is, e.g., a linearly stable attractor state. The former case has been called terminal dynamics and was first proposed to model a swift and robust dynamics of memory

recall in neuronal networks [38]. Such terminal dynamics might be quite common in living systems. For instance, the most common neuroscience model of decision making, the drift-diffusion model [16,17], is a terminal dynamics, as are a broad range of dynamical models for phenomena in cell-biology and morphogenesis [39–41]. We note in passing that exactly how frequently terminal dynamics are employed in living systems remains unknown.

In the deterministic limit, the entire spectrum of terminal dynamics can be covered by power-law dynamics of the form

$$\frac{d\tilde{L}}{dt} = -\gamma\tilde{L}^\alpha \quad (1)$$

with time constant $\gamma \geq 0$, exponent α , and $\tilde{L}$ is a measure of distance to the target state. All equations are understood to be nondimensionalized. Throughout the text, $\tilde{L}$ is used in forward-time dynamics and L (without the “~”) in reverse-time dynamics. For any $\alpha < 1$, the target state $\tilde{L}_{TS} = 0$ is reached in finite time with arrival times increasing with α and diverging at $\alpha = 1$ [Fig. 2(a)]. The pole at $\alpha = 1$ marks the transition to asymptotic convergence familiar from conventional fixed point attractors.

Interestingly, in a stochastic dynamics setting, a qualitative transition in the speed and robustness of target state approach occurs not at $\alpha = 1$ but rather at $\alpha = 0$ [Fig. 2(c)]. This transition is a fundamental feature of the Langevin equation generalizing Eq. (1),

$$d\tilde{L}(t) = -\gamma\tilde{L}^\alpha dt + \sqrt{D}dW_t, \quad (2)$$

with $\sqrt{D}$ the intensity of the fluctuations, and dW_t the Wiener process increment of zero mean $\langle dW_t \rangle = 0$ and delta covariance $\langle dW_t dW_{t'} \rangle = \delta(t - t')$.

For $\alpha = 0$ this Langevin equation represents the foundational model of decision making in cognitive neuroscience. For $\alpha = 0, -1$, and -2 it represents different competing models of cell division in animal cells. The case $\alpha = -1$ is the minimal form of a dynamics that has been proposed for the dynamics of associative memory recall in biological neural networks. Finally, $\alpha = 1$ serves as a minimal model of dynamics with a stable fixed point positioned at the target state, as is typically the case for the dynamics of gene regulatory networks.

The stochastic version of target state arrival is thus qualitatively different from its deterministic counterpart. For nonvanishing D , $\tilde{L} = 0$ is reached in finite time also for $\alpha \geq 1$ and the fixed arrival time is replaced by a hitting time distribution. This distribution is exactly solvable for $\alpha = 1, 0, -1$ [42–45] (see Sec. IV in the Supplemental Material [46]) and shown in Fig. 2(b). Mean hitting times can be obtained by simulations or alternatively by numerical integration of known integral expressions [37]. For the continuum of α -values between -2 and 1.5 , numerical simulations of the mean hitting time are displayed in Fig. 2(c).

Our analysis displayed in Fig. 2(c) reveals that terminal dynamics exhibits two distinct regimes of target state arrival: one with hitting times that are noise-insensitive and decreasing in the low noise limit ($\alpha < 0$), which we call *strongly terminal*, and another with slower, noise-sensitive hitting times that increase ($0 \leq \alpha < 1$) or diverge in the low noise limit ($1 \leq \alpha$),

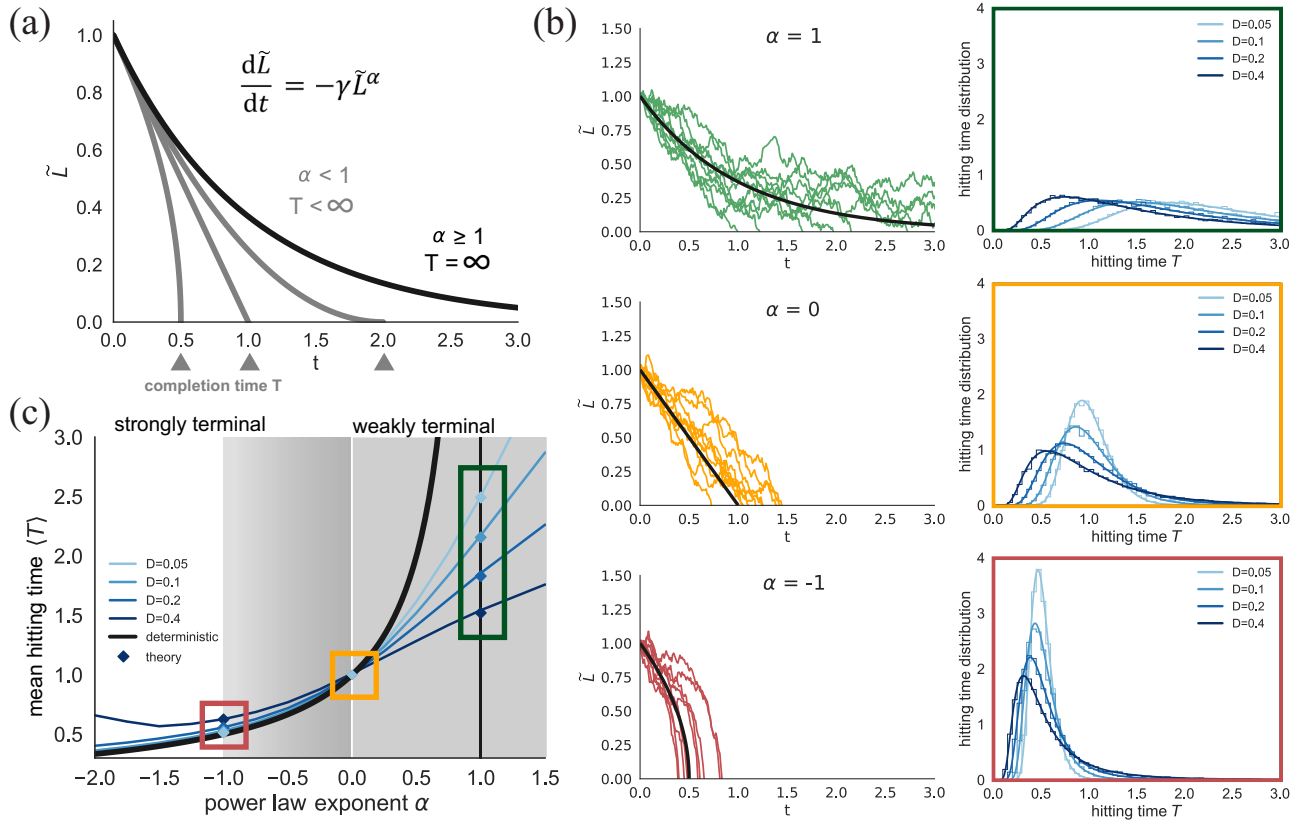


FIG. 2. Distinct regimes of stochastic terminal dynamics. Target state approach dynamics in biological systems needs to reach the target state in finite time. In stochastic terminal dynamics, completion times exhibit two regimes of distinct speed and robustness that we call weakly and strongly terminal. (a) Finite time completion in the deterministic dynamics Eq. (1). Solid lines depict solutions for $\alpha = -1, 0, 1/2$, and 1 . Arrows indicate completion times. Completion times are finite for $\alpha < 1$. (b) In stochastic systems, dynamics can complete in finite time even if their deterministic counterpart converges only asymptotically. Shown are solutions of Eq. (2) and the corresponding completion (hitting) time distributions for the three analytically tractable cases $\alpha \in \{-1, 0, 1\}$. (Left) Colored lines: simulated trajectories; black lines: deterministic solution. (Right) Hitting time distributions for different noise intensities D . Results of numerical simulations (histograms) are superimposed on the exact completion time distributions. (c) Mean completion times $\langle T \rangle$ as a function of power-law exponent α for different noise intensities. For comparison, the thick solid line depicts the deterministic limit. Numerical (solid lines) and exact (diamonds) results are superimposed. Colors mark different noise intensities. For $\alpha \geq 0$ fluctuations result in faster completion times compared to the deterministic limit. For $\alpha < 0$ fluctuations have no substantial impact on the completion time and only result in a slight slow down. The two regimes, called *weakly terminal* and *strongly terminal*, respectively, are separated by a white line. The gray value gradient marks a transition region between distinct phases of stochastic terminal dynamics (see Fig. 5). Biophysical models of the processes depicted in Fig. 1 cover both regimes and the boundary case: in models of cytokinesis, the effective force typically diverges near cell separation, the standard drift-diffusion model of decision making is a special case of Eq. (2) with $\alpha = 0$, and stationary states of gene regulatory networks are typically linearly stable and thus approach their target state as our model equation for $\alpha = 1$. All simulations are based on Eq. (2) with 20 000 realizations and parameters $\gamma = 1$, $L_0 = 1$.

called *weakly terminal* in the following. Notably, the example cases of (a) cytokinesis, (b) neural evidence accumulation, and (c) gene regulatory networks illustrated in Fig. 1 are representative of the two regimes and the border case [Fig. 2(c)]. Given the swift and robust target state convergence exhibited by strongly terminal dynamics, it appears particularly important to accurately identify this type of dynamics. As will become apparent in the following, this is not a trivial matter.

III. TARGET STATE ALIGNMENT INTRODUCES A STATISTICAL BIAS IN THE FORM OF A FICTITIOUS FORCE

Irrespective of dynamical regime, target state alignment represents the approach phases of an ensemble of trajectories in a natural temporal frame of reference: time to target state

arrival (time-to-completion). To expose fundamental properties of target state aligned (TSA) ensembles of trajectories, we first examine the special case of a process in which there is no directed dynamics at all,

$$d\tilde{L}(t) = \sqrt{D} dW_t, \quad (3)$$

equipped with an absorbing boundary at the target state $\tilde{L}_{TS} = 0$. Biological instances include random search dynamics, e.g., for the binding site of a transcription factor along a stretch of DNA [Fig. 3(a) [47–50]]. With distance to the binding site as the natural reaction coordinate, Fig. 3(b) depicts the construction and properties of this specific target state aligned ensemble. By construction, all sample paths of a target state aligned ensemble concentrate around the ensemble mean close to the target state. In the random search case, the mean

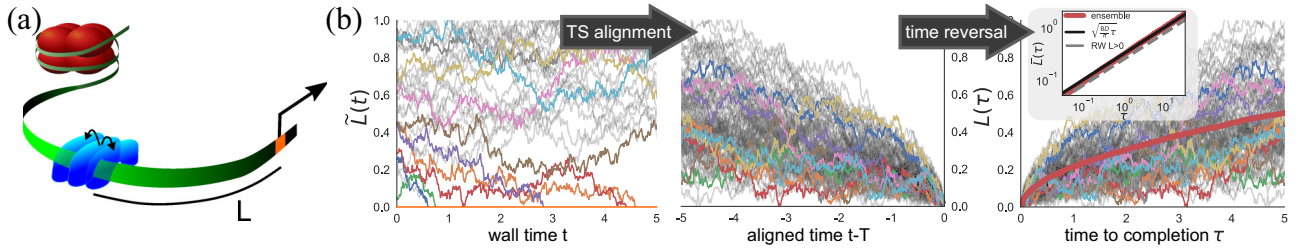


FIG. 3. In a time-to-completion frame of reference, even undirected stochastic dynamics appears as if fictitiously attracted into a target state. (a) Random walk (RW) -like sliding of transcription factor on a DNA segment with the promoter binding site (orange) as a target state. (b) (Left) Sample path realizations of a random walk with one reflecting and one absorbing boundary (orange) representing the promoter. (Middle) Target state aligned sample paths. (Right) Aligned and time-reversed ensemble of sample paths. The inset shows the square-root growth of the ensemble mean (red) in a log-log plot together with the correct target state aligned theoretical solution (black) derived in Sec. VI of the Supplemental Material [46]. Also displayed is the mean of a diffusion process in the half-space $L > 0$ starting from $L(0) = 0$ (dashed gray line), which has the same scaling but incorrect magnitude; see Sec. VI in the Supplemental Material [46]. The mean, growing with $\propto \tau^{1/2}$ (red line), might erroneously be taken to indicate the presence of a strongly terminal dynamics. Using target state aligned ensembles for dynamical systems inference thus requires separating such alignment-induced accelerating dynamics from genuine force components.

trajectory reaches the target state with an accelerating dynamics and infinite slope at the target state, as if strongly attracted into it. Applying the common low noise formula, equating the mean trajectory with the solution of the deterministic limit [37], to a target state aligned ensemble would in this case falsely suggest a strongly terminal dynamics while in fact there is only random motion [Fig. 3(b)].

IV. TARGET STATE ALIGNED ENSEMBLES CAN BE REPRESENTED AS MIXTURES OF BROWNIAN BRIDGES

To develop a mathematical representation of target state aligned ensembles for a general stochastic process defined by a Langevin equation of the form

$$d\tilde{L}(t) = f(\tilde{L})dt + \sqrt{D}dW_t, \quad (4)$$

where $f(\tilde{L})$ denotes a general force term, we first examined the formal mathematical structure of a target state aligned ensemble of trajectories using the concept of Brownian bridges. We summarized the full derivation of the exact target state aligned ensemble in Figs. 4(a)–4(c), showing the equations next to conceptual depictions of the respective dynamics. Each subfigure (a)–(c) essentially corresponds to one of the following sections.

Equation (4) together with a distribution of initial conditions $P^{\text{in}}(\tilde{L})$ defines an ensemble of trajectories $\tilde{L}_i(t)$ with wall-time t and lifetime T_i , where i denotes the index of the trajectory. The corresponding target state aligned time-reversed trajectories $L_i(\tau) = \tilde{L}_i(T_i - \tau)$ constitute the target state aligned ensemble and are distributed according to a joint probability density functional $R[L(\cdot), T]$. Here $L(\cdot)$ denotes the entire reverse-time trajectory and T its lifetime. $R[L(\cdot), T]$ provides a complete description of the target state aligned ensemble.

Constructing the marginal density $R(L, \tau)$, the instantaneous distribution of state variables in the target state aligned ensemble, uncovers that the target state aligned ensemble formally represents a mixture of different Brownian bridge subensembles. We demonstrate this graphically in Figs. 4(a) and 4(b), where the full ensemble both in forward time and after target state alignment and time reversal is displayed.

Three subensembles before and after time reversal are highlighted.

To obtain $R(L, \tau)$, two aspects are crucial: (i) the ensemble effectively evolves in reverse time, and (ii) the lifetime T of each trajectory is itself a random variable. As reverse time progresses, ever fewer trajectories remain in the ensemble. $R(L, \tau)$ is thus not normalized and its integral, the fraction of “live” -trajectories, decays with τ . In the absence of noise ($D = 0$), time-reversal of Eq. (4) is trivial. The equation of motion in reverse time is $dL(\tau) = -f(L)d\tau$. In a stochastic system, however, although the Wiener increment dW_t is time-reversal-invariant, inverting the sign of the right-hand side does not yield the correct time-reversed equation.

The correct reverse-time equation for an ensemble of fixed lifetime T [see Fig. 4(b)], as originally derived by Anderson [31], is given by

$$dL(\tau) = (-f(L) + f^G(L))d\tau + \sqrt{D}dW_\tau, \quad (5)$$

with

$$f^G(L) = D \frac{\partial}{\partial L} \ln(P^{\text{fw}}(L, T - \tau)) \quad (6)$$

a guiding force that depends on the solution $P^{\text{fw}}(\tilde{L}, t)$ of the forward Fokker-Planck equation

$$\frac{\partial}{\partial t} P(\tilde{L}, t) = -\frac{\partial}{\partial \tilde{L}} f(\tilde{L})P(\tilde{L}, t) + \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t). \quad (7)$$

It is the guiding force $f^G(L)$ that ensures the forward- and reverse-time dynamics are equivalent [31]. Hence, stating the time-reversed equation in principle requires knowledge of the solution of the forward process and its initial distribution. Although time-reversed dynamics might appear as a simple initial value problem, it is not.

To impose a target state, the Fokker-Planck equation has to be solved with an absorbing boundary condition at the target state. Equation (5) is valid for all trajectories of lifetime T and through Eq. (6) explicitly depends on the lifetime considered. Thus, in this representation, trajectories of distinct lifetimes follow different laws of motion and the entire ensemble represents an infinite mixture of Brownian bridge subensembles [see again Figs. 4(a) and 4(b)]. Hence, $R(L, \tau)$ for the aligned

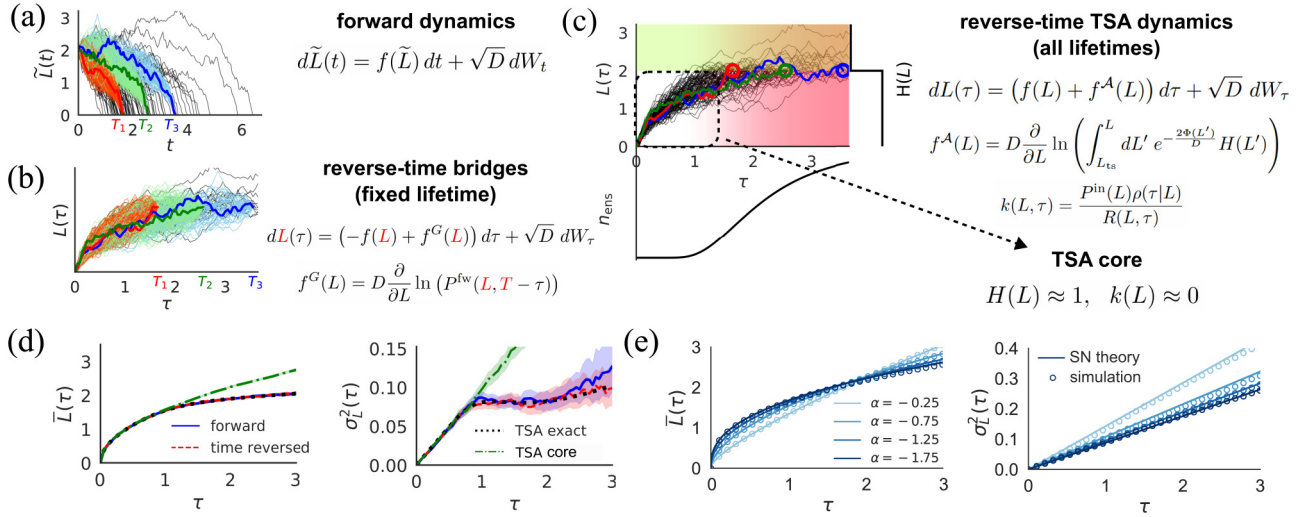


FIG. 4. Target state aligned ensembles are infinite mixtures of Brownian bridges that can be exactly described by a single effective reverse time dynamics. (a): The full forward ensemble is split into subensembles with different completion times T_i . Shown are three subensemble cases in red (T_1), green (T_2), and blue (T_3). One sample path per subensemble is highlighted (thick line). To the right, we show the forward-time Langevin equation (4) that governs the dynamics in the plot. (b) After target state alignment and time reversal, all subensembles together form the new ensemble $R(L, \tau)$. To the right, we show the reverse-time equation for a single bridge Eq. (5) and guiding force Eq. (6). The red color suggests that this equation is linked to the red bridge and does not simultaneously describe the other bridges as well. (c) Schematic depiction of the dependency of the reverse-time target state aligned dynamics Eqs. (9) and (11) on the forward initial condition $H(L)$ and the killing measure $k(L, \tau)$. In the white region, i.e., below the bulk of the initial distribution and prior to the domain of the killing measure, $f^A(L)$ is approximately independent of forward initial condition and lifetime distribution. Along the τ axis, the red gradient indicates that more and more trajectories are killed. To the right, we display the key equations of our target state alignment framework that describe the full reverse-time ensemble. The core of the target state aligned ensemble is obtained in the “white region” of the plot. (d) Comparison of ensemble mean and variance from forward simulations (blue), simulations of a mixture of Brownian bridges [51] (red), exact (black), and core (green) reverse-time target state aligned dynamics for $f(L) = -\gamma/L$. 95% bootstrap confidence intervals are shown for numerical results (see Secs. IV and V in the Supplemental Material [46]). Results were obtained using each 1000 sample path realizations with parameter settings $\gamma = 1$, $D = 0.2$, $\tilde{L}_0 = 2$. In the universal core of the ensemble, the approximate (green) reverse-time target state aligned dynamics exhibits an excellent agreement with the full solutions. (e) The small noise (SN) approximation (solid lines) well approximates results from numerical simulations (circles) for different α . The SN mean (top) was calculated using Eq. (21) and the SN variance (bottom) via Eq. (22) (see Sec. VI in the Supplemental Material [46]). We chose $\gamma = 1$, $D = 0.2$, $\tilde{L}_0 = 20$ here from 20 000 runs.

time-reversed ensemble is

$$R(L, \tau) = \int_{L_{\text{TS}}}^{\infty} dL_f P^{\text{in}}(L_f) \int_{\tau}^{\infty} dT R(L, \tau|T; L_f) \rho(T|L_f) \quad (8)$$

where $L_f = \tilde{L}_0$ is the initial condition of the forward process (now the final condition in reverse-time) (see Sec. II in the Supplemental Material for more details [46]). Three aspects of this construction are noteworthy. First, each sub-ensemble $R(L, \tau|T; L_f)$ only contributes to the complete ensemble for as long as τ does not surpass the subensemble’s lifetime T . This requirement is accounted for by the lower integration limit of the inner integral. Second, the relative weight of trajectories of this lifetime is given by the hitting time distribution of the forward process $\rho(T|L_f)$, which in turn depends on the forward initial condition. Third, the relative weight of each subensemble depends on the initial conditions of the forward process $P^{\text{in}}(L_f)$. The outer integral accounts for this by integrating over the distribution of initial values of the forward process.

Let us briefly consider the implications of the above result. The construction of the target state aligned ensemble $R(L, \tau)$ from subensembles of varying lifetimes T_i (and thus

varying guiding forces) seems to suggest that in general there is no unique stochastic differential equation which describes the full reverse-time dynamics. Different force laws seem to be active at the same state (L, τ) . At first glance this observation should raise substantial caution. With reverse time dynamics in principle being a mixture of different effective dynamics, can target state alignment really provide a strategy to infer directed biophysical dynamics? What is needed is a general understanding of under which conditions the target state aligned ensemble follows a unique stochastic differential equation.

V. REPRESENTING TARGET STATE ALIGNED ENSEMBLES IN REVERSE-TIME

Intuitively one expects that at least the final approach phase to the target state should be uniquely determined by the underlying dynamics and essentially be independent of forward initial conditions and lifetime distribution. If this intuition is valid, a representation of the target state aligned ensemble as a reverse time initial value problem with initial value $L(0) = \epsilon \rightarrow 0$ should exist. We demonstrate this by recasting the problem formulated in terms of bridge processes into an initial value problem where the dependency on T

and the forward initial conditions are treated as boundary conditions. In this representation, the emergence of the correct distributions of lifetimes and final values of reverse-time trajectories is achieved by the proper choice of a killing measure for terminating trajectories or correspondingly a sink for the reverse-time evolution of the marginal density [see Fig. 4(c)]. In the next section, we then demonstrate that spatially and temporally close to the target state these boundary conditions become negligible. The exact derivation is provided in Secs. II and III of the Supplemental Material [46].

In reverse time, the evolution of the marginal density $R(L, \tau)$ as shown in Sec. II of the Supplemental Material [46] is governed by the generalized Fokker-Planck equation

$$\frac{\partial}{\partial \tau} R(L, \tau) = -\frac{\partial}{\partial L} ((f(L) + f^A(L))R(L, \tau)) + \frac{D}{2} \frac{\partial^2}{\partial L^2} R(L, \tau) - P^{\text{in}}(L)\rho(\tau|L) \quad (9)$$

with the last term representing the time-dependent sink, given by the distribution of initial conditions and the hitting time distribution of the forward process $\rho(\tau|L)$. The “alignment and time-reversal force” $f^A(L)$ is given by

$$f^A(L) = D \frac{\partial}{\partial L} \ln \left(\int_{L_{\text{TS}}}^L dL' e^{-\frac{2\Phi(L')}{D}} H(L') \right) \quad (10)$$

with the potential $\Phi(L) = \int_{L_{\text{TS}}}^L f(L') dL'$ and $H(L) = 1 - \int_{L_{\text{TS}}}^L P^{\text{in}}(L') dL'$ the complementary cumulative probability of initial conditions. The generalized Fokker-Planck equation (9) corresponds [52–55] to the stochastic differential equation

$$dL(\tau) = (f(L) + f^A(L))d\tau + \sqrt{D} dW_\tau, \quad (11)$$

equipped with killing measure

$$k(L, \tau) = \frac{\rho(\tau|L)P^{\text{in}}(L)}{R(L, \tau)}. \quad (12)$$

Here, the killing measure completely describes the termination of trajectories at their forward initial conditions equivalent to the sink term in Eq. (9). For finite target state aligned ensembles comprised of N_{ens} sample paths, this implies that the killing measure terminates $n_{\text{ens}} k(L, \tau) d\tau$ of the remaining n_{ens} sample paths at each timestep $d\tau$ [Fig. 4(c)].

Representing the finite trajectory lifetimes in this way also simplifies the alignment forces: In Eq. (10) the alignment is captured by a single time-independent alignment force rather than by time-dependent guiding forces as in Eq. (6). The force $f^A(L)$ simultaneously mediates the time reversal of the genuine force law and captures the impact of both the forward initial condition as well as any fictitious force component arising from target state alignment. Similar to a Coriolis force in mechanics, which represents all effects of transforming to a rotating frame of reference by a single, additive, time-invariant force component, the alignment force describes all effects of transforming to a target state aligned frame of reference including time reversal. Distinct from a Coriolis force, it also depends on the force law of the genuine dynamics, and combines it with the intensity of diffusion and the distribution of initial conditions.

VI. THE SPACE-TIME CORE OF A TARGET STATE ALIGNED ENSEMBLE IS INDEPENDENT OF FORWARD INITIAL CONDITIONS

The above reverse-time representation now constitutes an exact description of a full ensemble of aligned trajectories [Fig. 4(c)], however it still depends on initial conditions of the forward process. For application in biological systems with uncertain onset conditions, we next isolate a *universal space-time core* within the total target state aligned ensemble that is independent of forward initial conditions and exactly captures the dynamics close to the target state [Fig. 4(c)].

The existence of a universal space-time core is most easily demonstrated by inspecting the killing measure Eq. (12). For L below the bulk of the forward initial distribution and τ smaller than the minimal typical lifetime both factors of the killing measure vanish, i.e., $P^{\text{in}}(L) \approx 0$ and $\rho(\tau|L) \approx 0$. The resulting approximate stochastic differential equation then completely describes the target state aligned ensemble close to the target state in space and time as an actual initial value problem in reverse time with initial value $L(0) = \epsilon \rightarrow 0$. Because very short lifetimes are exponentially suppressed, the probability density functional close to the target state satisfies $R[L(\cdot), T] \approx R^\circ[L(\cdot)]$ to a very good approximation. Thus $R^\circ[L(\cdot)]$ represents a universal core of the target state aligned ensemble that is lifetime independent and insensitive to forward initial conditions [Fig. 4(c)]. Intriguingly, during the target state approach the ensemble of trajectories “forgets” its forward initial condition in finite time.

In the range of validity of this approximation, the alignment force shaping the universal core structure substantially simplifies. For a power-law dynamics Eq. (1) we obtain (see Sec. V in the Supplemental Material [46])

$$f^A(L) = \frac{(D\alpha + D) \left(-\frac{2\gamma}{D\alpha + D} \right)^{\frac{1}{\alpha+1}} e^{\frac{2\gamma L^{\alpha+1}}{D\alpha + D}}}{\Theta(\alpha + 1) \Gamma\left(\frac{1}{\alpha+1}\right) - \Gamma\left(\frac{1}{\alpha+1}, -\frac{2L^{\alpha+1}\gamma}{\alpha D + D}\right)}. \quad (13)$$

Here $\Gamma(L)$ is the gamma function, $\Gamma(n, L)$ the upper incomplete gamma function, and $\Theta(n)$ is the Heaviside function. Equation (13) is valid for $\alpha \neq -1$, with the form $f^A(L) = \frac{2\gamma + D}{L}$ at $\alpha = -1$ continuously connecting both domains of validity. For $\gamma = 0$, i.e., pure diffusion, Eq. (12) simplifies to $f^A(L) = \frac{D}{L}$ explaining the resemblance between target state aligned diffusion and deterministic terminal dynamics with $\alpha = -1$ [Fig. 3(b)].

We illustrate the validity of the above derivations for the case $\alpha = -1$ by comparing analytically obtained moments with numerical simulations [Fig. 4(d)]. Our comparison in Fig. 4(d) demonstrates that ensemble mean and variance calculated based on Eq. (13) agree excellently with the exact solution in the universal core of target state aligned ensembles (see Secs. IV and V in the Supplemental Material [46]).

VII. OPAQUE-TO-TRANSPARENT PHASE TRANSITION

The approximation Eq. (13) enabled us to analytically determine the universal core structure of target state aligned ensembles for stochastic terminal dynamics Eq. (2). Close to the target state in space and time, the joint probability density $R^\circ(L, \tau; L', \tau')$ remains normalized and completely captures

the structure of the ensemble. We thus calculated its leading order moment functions

$$\bar{L}(\tau) = \int_0^\infty dL R^\circ(L, \tau) L, \quad (14)$$

$$\sigma_L^2(\tau) = \int_0^\infty dL R^\circ(L, \tau) [L - \bar{L}(\tau)]^2, \quad (15)$$

$$\begin{aligned} C_L(\tau, \tau') &= \int_0^\infty dL dL' R^\circ(L, \tau; L', \tau') [L - \bar{L}(\tau)] [L' - \bar{L}(\tau')] \\ &= \sigma_L(\tau) \sigma_L(\tau') c_L(\tau, \tau'), \end{aligned} \quad (16)$$

with the covariance function $C_L(\tau, \tau')$ decomposed into variance $\sigma_L^2(\tau)$ and correlation function $c_L(\tau, \tau')$. As the ensemble is nonstationary, not only is the mean time-dependent but the two-time covariance function explicitly depends on both time arguments, rather than on the time lag $|\tau - \tau'|$. Notably in a Gaussian approximation, $\bar{L}(\tau)$ and $C_L(\tau, \tau')$ completely characterize the ensemble and are its sufficient statistics. In principle, these statistics could thus provide all the information needed for the complete identification of the underlying dynamics and are key properties to assess inference and identifiability of target state directed dynamics.

Using a small L approximation of the alignment force Eq. (13), both the mean and covariance function can be analytically evaluated for $\alpha \geq 0$ and for $\alpha < -1$ (see Sec. VI in the Supplemental Material [46]). Intriguingly, these distinct sectors, belonging to the weakly and strongly terminal regime, respectively (see Fig. 2), exhibit diametrically opposed behavior. For $\alpha \geq 0$, the small L approximation maps the universal core structure onto the case of pure diffusion (see Sec. VI in the Supplemental Material [46]), and we find

$$\bar{L}(\tau) = \sqrt{\frac{8D}{\pi}} \tau, \quad (17)$$

$$\sigma_L^2(\tau) = \frac{(3\pi - 8)D\tau}{\pi}, \quad (18)$$

$$c_L(\tau, \tau') = \begin{cases} \frac{2g(\tau, \tau')}{(3\pi - 8)\sqrt{\tau\tau'}} & \tau < \tau' \\ 1 & \tau = \tau' \\ \frac{2g(\tau', \tau)}{(3\pi - 8)\sqrt{\tau'\tau}} & \tau > \tau'. \end{cases} \quad (19)$$

with

$$\begin{aligned} g(\tau, \tau') &= -4\sqrt{\tau\tau'} + 3\sqrt{\tau(\tau' - \tau)} \\ &\quad + (2\tau + \tau') \sin^{-1} \left(\sqrt{\frac{\tau}{\tau'}} \right). \end{aligned} \quad (20)$$

Note that Eqs. (17) and (18) also correctly describe the target state aligned ensemble depicted in Fig. 3(b). Distinctly, for $\alpha < -1$ we obtain

$$\bar{L}(\tau) = [(1 - \alpha)\gamma\tau]^{\frac{1}{1-\alpha}} + D \frac{(7\alpha - 3)[(1 - \alpha)\gamma\tau]^{\frac{\alpha}{1-\alpha}}}{4(3\alpha - 1)\gamma}, \quad (21)$$

$$\sigma_L^2(\tau) = D \frac{1 - \alpha}{1 - 3\alpha} \tau, \quad (22)$$

$$c_L(\tau, \tau') = \left(\frac{\min[\tau, \tau']}{\max[\tau, \tau']} \right)^{\frac{3}{2} + \frac{1}{\alpha-1}}, \quad (23)$$

which is also valid for the intermediate range $-1 \leq \alpha < 0$ in the low noise limit $D \ll 1$ (see Sec. VI in the Supplemental Material [46]). Figure 4(e) depicts results obtained with

a small noise (SN) approximation and demonstrates the excellent agreement with numerical simulations.

The structure of the ensemble thus fundamentally transforms at the transition from the weakly terminal to the strongly terminal regime (compare Fig. 2). In the weakly terminal regime, the moments depend only on the noise intensity, D , and are otherwise given by universal functions independent of all parameters of the genuine force term [Figs. 5(a) and 5(b)]. In contrast, in the strongly terminal regime, all parameters of the dynamics can be readily obtained from the moment functions [Figs. 5(c) and 5(d)]. The correlation function depends on the power-law exponent α . Given α , the variance function fixes the noise intensity D and the mean in turn fixes the time constant γ .

As $\alpha = 0$ is passed from below, the core structure of the ensemble transforms from being completely informative about the underlying dynamics to an uninformative invariant form. Accordingly, we propose to term these distinct phases of target state aligned ensembles *transparent* and *opaque*, respectively. Inference based on the fundamental statistics $\bar{L}(\tau)$ and $C_L(\tau, \tau')$ will be well conditioned in the transparent and impossible or severely underpowered in the opaque phase. Figures 5(a)–5(d) confirm the strong and weak parameter dependencies of the moment functions near the target state in the contrasting regimes, and Fig. 5(f) depicts the magnitude of the informative component of the moment functions that emerges at the transition to the strongly terminal regime.

Our results predict that the marginal density function for small τ is invariant in the opaque phase and collapses to a delta distribution in the transparent phase [Fig. 5(e)]. A scalar order parameter for this phase transition thus is the square coefficient of variation C_V^2 of the marginal density function. While it converges for small τ to 0 for $\alpha < -1$, it is given by the constant $C_V^2 = 3\pi/8 - 1$ in the weakly terminal regime. For small but finite τ , C_V^2 exhibits an extended, D -dependent transition region in the range $-1 \leq \alpha < 0$. For $\alpha = -1$ (Bessel process) we find $C_V^2 = \frac{2D\Gamma(5/2 + \gamma/D)^2}{(3D + 2\gamma)\Gamma(2 + \gamma/D)^2} - 1$. Figure 5(e) displays this collapse of the marginal distribution across the transition. Figures 5(g) and 5(h) illustrate ensembles in the opaque and transparent phase in forward time and the characteristic D dependence of their ensemble means.

VIII. CORE-BASED INFERENCE FROM TARGET STATE ALIGNED ENSEMBLES

The fact that the core structure of a target state aligned ensemble, captured by the leading moment functions near the target state, is uninformative in the opaque phase does not imply that the genuine dynamics is completely hidden. To decode it, however, nonuniversal features of the leading order moments at larger τ of the ensemble should be used. A method that is sensitive to moments of all orders is sample path based inference. We thus adapted the Onsager-Machlup formalism for statistical inference from a target state aligned ensemble of sample paths (see Sec. VIII in the Supplemental Material [46]). Key to this is the proper inclusion of the alignment forces in the likelihood. For systems with terminal dynamics, Eq. (13) provides a suitable basis for target state aligned path inference with the

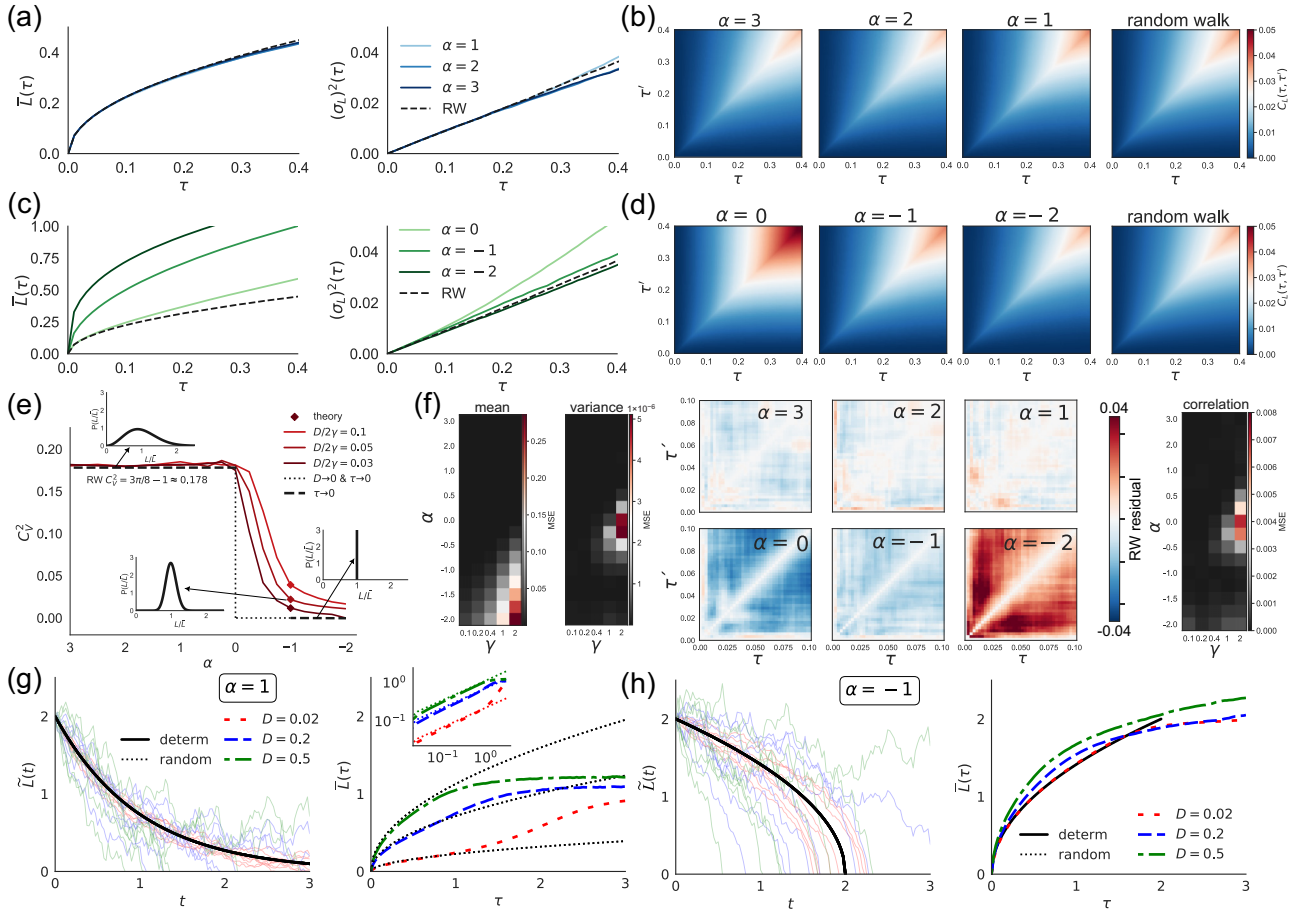


FIG. 5. The universal core structure of target state aligned ensembles undergoes an opaque-to-transparent phase transition as dynamics change from weakly to strongly terminal. The universal core structures for weakly terminal dynamics all collapse onto the statistics of a random walk close to the target state while strongly terminal dynamics can be decoded from its low order moment functions. (a) Numerically estimated mean- (left) and variance-functions (right) for $\alpha = 1, 2, 3$ compared to the analytically derived universal core of target state aligned ensemble result (dashed line). (b) Same for two time covariance functions for the examples shown in (a). (c) Numerically estimated mean (left) and variance (right) for $\alpha = 0, -1, -2$. For strongly terminal dynamics ($\alpha = -1, -2$) both moment-functions are distinct from those of a random walk (dashed line) even close to the target state. In the transition case ($\alpha = 0$) mean and variance approach the random-walk moments as $\tau \rightarrow 0$. (d) Covariance functions for the strongly terminal examples shown in (c). In contrast to (b), the covariance functions for $\alpha = 0$ substantially differ from the random-walk covariance function. (e) Order parameter C_γ^2 as a function α across the opaque-to-transparent phase transition. Analytical results obtained for the universal core and low noise approximation are shown by dashed lines. Solid lines show numerically obtained results close to the target state ($\tau = 0.01$). Diamonds indicate analytical results for $\alpha = -1$. Three insets depict the analytically obtained form of the marginal densities near the target state. (f) (Left) The mean squared amplitude of the informative deviation between the actual moment functions and the corresponding random-walk result for $0 < \tau < 0.2$ are shown as a phase diagram in the α - γ plane. (Middle) Deviation of the correlation functions from the random-walk result for the cases displayed in (b), (d). (Right) Mean square amplitude of the informative deviation of two time correlation functions from the random-walk result for $0 < \tau < 0.2$ shown as a phase diagram in the α - γ plane. The phase diagrams demonstrate that an informative component of the low order moment functions emerges at the opaque-to-transparent phase transition. Numerical results were obtained from 20 000 trajectories; $D = 0.2$ and $\gamma = 1$ if not indicated otherwise. (g), (h) Noise-dependences of target state aligned ensembles differ between transparent and opaque phases. (g) (Left) Ensembles of trajectories in forward time for different noise intensities. (Right) The mean $\bar{L}(\tau)$ for three different noise intensities (dashed lines) compared to random-walk results (finely dashed lines). For the universal core structure ($\tau < 1$, close to target state), the moment functions are indistinguishable from the random-walk results and α -independent. Log-Log inset: $\bar{L}(\tau) \sim \tau^{1/2}$ independent of the noise strength D . (h) Same as (g) for $\alpha = -1$. In the universal core of the target state aligned ensemble ($\tau < 1$, close to target state), the mean $\bar{L}(\tau)$ (dashed line) systematically deviates from the deterministic limit as the noise intensity D increases (black line).

log-likelihood

$$\ln \mathcal{L} = -\frac{N_{\text{ens}} N_\tau}{2} \ln(2\pi D \Delta \tau) - \sum_{j=1}^{N_{\text{ens}}} \sum_{i=0}^{N_\tau-1} \frac{(L_{i+1}^{(j)} - L_i^{(j)} - f^{\text{TSA}}(L_i^{(j)}) \Delta \tau)^2}{2D \Delta \tau}, \quad (24)$$

where the force is given by $f^{\text{TSA}}(L) = f(L) + f^A(L)$. Here, N_{ens} denotes the number of trajectories and N_t the number of time steps.

While the path likelihood allows for genuine Bayesian inference and model selection, a simpler approach is to use a *moment* strategy, based on the mean square residuals between empirical ensemble mean and model mean $R_{\mu,i} = x_i - \bar{L}(\tau_i)$ and analogously for the variance $R_{\sigma,i} = y_i - \sigma_L^2(\tau_i)$. Here x_i, y_i are the data derived empirical mean and variance at times τ_i . The model moments can be obtained via numerical simulation, from exact analytical calculations or our small noise theory. The moment loss function reads

$$\mathcal{L} = - \sum_{i=1}^{N_t} (R_{\mu,i}^2 + R_{\sigma,i}^2). \quad (25)$$

Its region of sensitivity is mapped out in the phase diagram Fig. 5(f).

In practical application, with real biological data, measurement noise can significantly alter inference results and has to be accounted for. For example, using increment-covariance analysis, measurement noise can be estimated and statistical moments subsequently corrected [56]. How to exactly deal with measurement noise depends on the specifics of the system, and a thorough discussion is beyond the scope of the present paper. However, for the simple case of homogeneous Gaussian measurement noise, we present a suitable extension to the path-based likelihood in Sec. VIII of the Supplemental Material [46].

IX. TERMINAL DYNAMICS IN CYTOKINESIS

We tested these two inference approaches in a case study on the dynamics of cytokinesis (Fig. 6). Cytokinesis is a process in cell biology for which distinct biophysical mechanisms predict characteristically different terminal dynamics. The force that is driving cytokinesis is mediated by a contractile ring of myosin motors and actin filaments of concentrations c_M and c_A . Both types of force generating molecules turn over with cytosolic pools. As the active tension in the contractile ring is proportional to $c_M c_A^2$, the timescale of myosin and actin turnover strongly impact the dynamics. If turnover for both is fast, concentrations are independent of the ring perimeter during constriction leading to an $\alpha = 0$ behavior [Fig. 6(a)]. If, however, either myosin or actin exhibit long residence times in the ring, their respective ring-bound concentrations strongly increase during constriction, leading to $\alpha = -1$ or -2 behavior, respectively [Fig. 6(a)]. Distinct types of terminal dynamics are thus predicted depending on the timescales of turnover between bound and cytosolic fractions. Further details on how the effective Langevin dynamics arises from different regimes of actomyosin dynamics are described in Sec. VII of the Supplemental Material [46].

To test the power of our core-based inference strategies to correctly identify these regimes from time-series data, we computationally generated cytokinetic constriction trajectories using a model by Zumdick *et al.* [57], which covers all three scenarios (see Sec. VII in the Supplemental Material [46]). Starting from an equilibrium perimeter, the dynamics of ring constriction fades in and subsequently drives progressive ring constriction and final cell separation. Internal fluctuations

of the ring perimeter were modeled by an additive noise source.

For Bayesian inference of the underlying actomyosin turnover regime together with the parameters of an effective model from an ensemble of constriction trajectories, we first evaluated the path likelihood for the target state aligned ensemble forces and for each of the three scenarios with $\alpha = 0, -1, -2$ (for details, see Secs. VII and VIII in the Supplemental Material [46]). The correct case $\alpha = -1$ was clearly singled out by the highest evidence, a Bayesian measure of model comparison [58] [Fig. 6(b)]. We confirmed that the moments of the inferred model exactly match the cytokinesis data generated from Zumdick's model [Fig. 6(d)]. The other turnover regimes were also unambiguously identified (see Sec. VII in the Supplemental Material [46]).

We further assessed the precision and accuracy of path- and core-based inference in situations in which either the number of trajectories N_{ens} or the temporal sample number per trajectory N_t is limited [Fig. 6(c)]. We found that both moment based inference and path inference can infer the correct parameters with high precision for high sampling rate and trajectory number. For high time step numbers $N_t \gg 1$ only, but not necessarily high number of trajectories, the path inference is unbiased and correctly infers quantitative parameters even in the low trajectory number limit. Conversely, for large numbers of trajectories $N_{\text{ens}} \gg 1$ the ensemble method is unbiased, and even for low temporal sampling, here $N_t = 6$, γ can be reliably inferred. We conclude that, even with limited data, the specific regime of actomyosin turnover is readily and specifically detectable using dynamical systems inference based on our target state aligned ensemble theory.

X. DISCUSSION

In biology, the large-scale datasets that can now be acquired should spur our knowledge and understanding of target state directed dynamics through data-driven inference. Despite the recent discovery of new and powerful time series based inference approaches [59,60], target state directed dynamics have remained severely understudied. Our analysis reveals that key to the analysis of target state directed dynamics is the seemingly innocent step of trajectory temporal alignment. Alternative to our target state alignment approach, one might choose to align individual trajectories at process onset, an implicit requirement for most canonical system modeling approaches. In practice, however, these alternative reference times often cannot be defined with similar certainty. Stochastic variability makes it hard in general to even roughly determine the onset time for each individual sample path. In particular during fade-in and onset, systems may exhibit substantial sample-to-sample heterogeneity. By contrast, our analysis directly demonstrates that near target state arrival the relevant dynamical behavior can be expressed most purely and uniformly. In addition, target states, such as the example of daughter cell separation in cytokinesis [57,61,62], often are unique and can be accurately detected. We note that stochastic dynamics that terminate at specific points in time are ubiquitous in our world and not only confined to the realm of biology. One may think of bankruptcies in financial dynamics, for example.

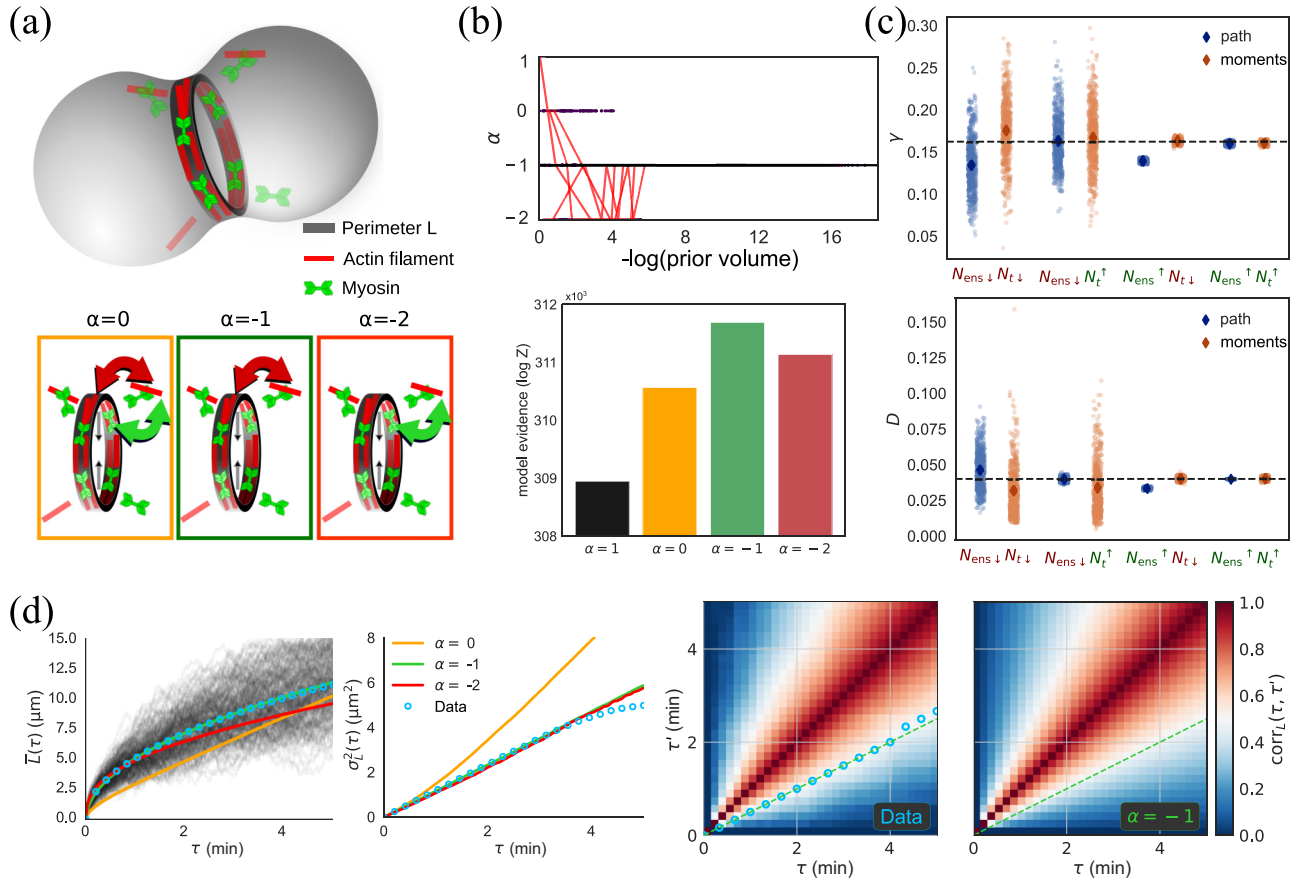


FIG. 6. Reverse time inference of terminal dynamics uncovers distinct regimes of actomyosin turnover from time-series of cytokinetic ring constriction. (a) Schematic of three different regimes of actomyosin turnover resulting in distinct kinetics of cytokinesis: Constant active tension for high actin and myosin turnover ($\alpha = 0$, orange), $1/L^2$ -active tension for stalled myosin-turnover ($\alpha = -1$, green) and $1/L^2$ -active tension for stalled actin-turnover ($\alpha = -2$, red). (b) Using path-ensemble maximum *a posteriori* inference via nested sampling [58] (see Sec. VIII in the Supplemental Material [46]), the dynamical law leading to constriction is unambiguously inferred for finite target state aligned ensembles of constriction trajectories. (Top) Convergence (decrease in parameter prior volume) of the inference for the estimation of parameter α . (Bottom) Bayesian evidence clearly identifies the correct type of strongly terminal dynamics. (c) Precision and accuracy of inferred parameters qualitatively differ between path and moment based inference depending on data properties. Trajectory data were altered by reducing the number of trajectories in the ensemble N_{ens} and the number of sample points per trajectory N_t . In the low data limit we chose $N_{\text{ens}} \downarrow = 2$ and $N_t \downarrow = 5$, whereas for the data-saturated limit we used $N_{\text{ens}} \uparrow = 900$ and $N_t \uparrow = 1000$. Depicted is the scatter of maximum *a posteriori* estimates from 50 inference runs with N_{ens} randomly drawn trajectories. Path inference is superior to ensemble-based inference statistics for high sampling rate and low number of trajectories $N_{\text{ens}} \downarrow = 2$. Inference using the moments strategy is recommended for high numbers of trajectories, as it achieves good results even for very low sampling rates $N_t \downarrow = 5$. (d) Confirmation of the inferred force law ($\alpha = -1$) by comparing mean- and variance-functions obtained from simulations for three maximum *a posteriori* parameter sets conditioned on the correct and two incorrect α values. The two-time correlation functions of the constriction trajectories and the correlation functions predicted by the inferred dynamics are in perfect agreement. To facilitate comparison, one equi-correlation line for both is marked (trajectories: blue circles, $\alpha = -1$: green dashed line).

Analyzing target state directed dynamics not in forward time, measured from process onset, but in reverse time, as examined in our study, is the preferable choice in terms of temporal precision and ensemble purity. While target state alignment has been used for statistical time-series analyses in fields from the physics of biopolymers [27] to cognitive neuroscience [30], the theoretical foundations of target state alignment based dynamical systems inference have so far never been systematically analyzed and, as we have seen, naive application of trajectory alignment can easily lead to erroneous system identification (Fig. 3).

Because target state convergence is temporally confined to short snippets of time, inferring target state directed dynamics

must be expected to pose special challenges for dynamical systems inference. It is intriguing that these challenges materialize as a phase transition from opaque to transparent inference phases, located at the transition from weakly to strongly terminal dynamics. At first sight, the swift target state approach of strongly terminal dynamics might appear prone to hiding its signatures from inference. Essentially due to its enhanced stereotypy, however, target state alignment effectively concentrates the signatures of strongly terminal dynamics in low order moments of the target state aligned ensemble. For weakly terminal dynamics, the genuine force decays towards the target state and is thus overshadowed by the diverging fictitious alignment force. Compared to thermodynamic phase

transitions, the opaque inference phase in this sense resembles a high temperature phase in which random motion dominates over any specific interaction. Compared to the classical limitations to statistical inference, the opaque-to-transparent phase transition is a qualitatively novel phenomenon. First, all parameters of our model dynamics are formally identifiable. Second, limitations of parameter inference and statistical model selection generally result from a finite data volume and vanish in the infinite data limit. Our analysis, however, demonstrates that the opaque-to-transparent phase transition persists in the infinite data limit.

Beyond the universal core, the target state aligned ensemble is, on the one hand, informative about the genuine dynamics, but on the other hand it is potentially contaminated by the fade-in effects mentioned above. Decoding target state directed dynamics in the opaque phase thus provides an important direction to further develop the use of our target state alignment path inference approach and an interesting challenge for the data-driven inference of target state directed dynamics in general.

Strongly terminal dynamics equip living systems with the means to swiftly and robustly reach target states and, according to our results, are readily identifiable. In which living systems should one expect strongly terminal dynamics to occur? In the cytokinesis example, the root cause for the emergence of terminal dynamics is the spatial confinement of force generating molecules in a shrinking volume. In cell biology, spatial movement and confinement of effector and signaling molecules are not uncommon [63,64] and large-scale spatial and topological transformations that can concentrate effectors occur frequently in morphogenesis [65,66]. Target state directed processes in cell and developmental biology are thus prime candidates for strongly terminal dynamics. Historically, terminal dynamics were first postulated in the cognitive domain to equip the process of memory recall with enhanced speed and robustness [38]. The drift-diffusion model of decision making under uncertainty [16,17] sits right at the transition from weakly to strongly terminal dynamics. In cognitive processes, strongly terminal dynamics might primarily be employed when swift action is essential, such as when making a decision fast is more beneficial than making the best possible choice.

Our current theoretical framework rigorously addresses effective one-dimensional dynamics. However, projecting high-dimensional systems onto low-dimensional reaction coordinates can introduce non-Markovian behavior [67,68]. In many cases, Markovian approximations remain valid, for example in high-dimensional Brownian motion, projected onto the radial distance between the diffusing particle and its target (e.g., a ligand-receptor pair). This projection interestingly introduces a repulsive entropic force proportional to D/r that can prevent target state arrival in three dimensions but not in two [44]. In principle, our framework is agnostic about dimensionality since the Fokker-Planck and reverse-time theory, which are the basis of our framework, can be extended to higher dimensions. Work in stochastic neuronal dynamics in the presence of multiple intrinsic timescales has pioneered Fokker-Planck-based theories and approximation schemes for systems with one degree of freedom, determining terminal state arrival coupled to multiple degrees

of freedom with distinct timescales [69–72]. These studies suggest that our time-reversal formalism can in principle be extended to high-dimensional systems with target states described by lower-dimensional manifolds.

When high-dimensional dynamics are evolving in some potential landscape, the key question is whether an effective, slow-timescale dynamic can be separated from faster residual dynamics, often allowing the latter to be treated as additive multiplicative noise [73]. In systems lacking clear timescale separation, projection onto effective coordinates yields memory kernels, complicating time-reversal analysis [67,68]. For an exact treatment of such systems, it is conceivable to develop a path-integral-based theory of TSA ensembles. In a perturbative approach, such treatment would effectively start with our path likelihood description Eq. (24), since $\mathcal{L}$ becomes the functional density of the TSA ensemble in the continuum limit. In cases in which short-lived memory effects may be negligible, while slowly varying memory kernels over times longer than typical completion times, non-Markovian features are expected to manifest as trajectory-specific heterogeneity, effectively acting as quenched disorder. Thus a systematic approach to TSA ensembles with parameter heterogeneity and corresponding inference approaches provide an additional avenue to establish generalizations of our theory for applications in non-Markovian dynamics.

From a practitioner's point of view, the target state alignment approach introduces a new perspective to the design of experiments. It lowers the burden of controlling suitable initial conditions and facilitates the investigation of directed dynamics under conditions that are as natural as possible. Simulations of molecular dynamics with a well-defined reaction coordinate, e.g., receptor-ligand binding, represent another promising area to apply the target-state perspective. In conventional binding simulations, the event is so rare that obtaining even a few successful trajectories is prohibitively expensive. Our reverse-time formulation suggests an alternative: treating the bound complex as the initial condition and propagating the dynamics backward in time. In contrast to Anderson's original construction [31], which relies on sampling or learning the forward probability density, our TSA core structure ensures the correct reverse-time physics without requiring knowledge of the forward initial conditions. Therefore, TSA-based dynamics might help to open new, efficient routes for exploring rare-event molecular dynamics and other dynamics captured by chemical reaction coordinates.

We anticipate that a thorough understanding of target state aligned ensembles and inference phases will be essential to reveal the hidden laws that guide target state directed processes in living systems.

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S.E., N.L., M.H., and F.W. conceived this work. N.L. performed analytical derivations and derived close-to-target state and low noise approximations. N.L. and M.H. performed

numerical calculations. J.G. and F.W. obtained funding. S.E. and F.W. were responsible for supervision. All authors wrote the original draft. F.W., M.H., and N.L. reviewed and edited the final manuscript with input from all authors.

DATA AVAILABILITY

The code used to generate the inference results is openly available at [93].

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