

Supplementary Information - The Landscape of Target State Directed Processes in Living Systems

Nicolas Lenner^{1,2,3†}, Matthias Häring^{1,4}, Stephan Eule^{1,5}, Jörg Großhans^{4,6} and Fred Wolf^{1,4,7,8,9,10†}

¹Max-Planck-Institute for Dynamics and Self-Organization, Göttingen, Germany; ²Simons Center for Systems Biology, School of Natural Sciences, Institute for Advanced Study, Princeton, New Jersey, USA; ³Jonathan M. Nelson Center for Collaborative Research, Institute for Advanced Study, Princeton, New Jersey, USA; ⁴Göttingen Campus Institute for Dynamics of Biological Networks, Göttingen, Germany; ⁵German Primate Center, Göttingen, Germany ⁶Department of Biology, Philipps University Marburg, Germany; ⁷Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany ⁸Institute for the Dynamics of Complex Systems, University of Göttingen, Göttingen, Germany ⁹Center for Biostructural Imaging of Neurodegeneration, Göttingen, Germany ¹⁰Bernstein Center for Computational Neuroscience Göttingen, Göttingen, Germany

† Lenner@ias.edu, Fred.Wolf@ds.mpg.de

This supplemental material provides the technical background of the theory of target state aligned (TSA) dynamics and examples discussed in the main paper. We present the derivation of the reverse time target state aligned stochastic differential equation (TSA SDE), analytically explore the influence of the forward initial conditions on the reverse time dynamics and study the genuine form of TSA dynamics close to the target state. For each step in the derivation we provide analytically tractable examples and show how the theory can be applied to infer genuine forces from dynamics of biological examples. In particular, we demonstrate how different scenarios of cytokinetic ring constriction, that is the separation of a cell into two daughter cells, can be inferred. We start with a self containing summary of relevant concepts for stochastic processes in reverse time.

CONTENTS

I. Stochastic dynamics setting	3
A. Markov processes	3
B. SDE and Fokker Planck representations	3
II. Time reversal and alignment	4
A. The reverse time Fokker-Planck equation	5
B. The time reversal of a terminating sub-ensemble	8
1. The target state bridge normalization	9
2. Backward Fokker-Planck for hitting time distribution	10
C. The time reversal and alignment of the full terminating ensemble	10
D. Derivation of the reverse time TSA Fokker Planck equation	13
III. Normalized TSA dynamics	16
A. Derivation of the normalized TSA dynamics	17
IV. Exactly solvable reverse time dynamics	18
A. Constructing the TSA ensemble from its definition – the random walk	18
B. Sampling TSA ensembles via reverse time random bridges	19
1. Bessel process	20
2. Advected random walk	20
3. Ornstein-Uhlenbeck type process	22
C. Constructing TSA ensembles from their reverse time TSA Fokker-Planck equation – the Bessel process	23
V. TSA dynamics close to the target state	24
A. TSA dynamics independent from forward initial conditions	25
B. Comparing TSA dynamics with and without forward initial conditions	26
1. Bessel process	26
2. Advected random walk	27
3. Ornstein-Uhlenbeck type process	28
VI. Small L and weak noise approximation – Strongly and weakly terminal TSA dynamics	28
A. The derivation of the small L expansion	29
1. The case $ z \rightarrow 0$	29
2. The case $ z \rightarrow \infty$	30
3. The L and D dependent range $-1 < \alpha < 0$	30
B. Moments and universal correlation function for weakly terminal TSA ensembles	32
C. Moments for strongly terminal TSA ensembles	33
1. Weak noise approximation of moments for strongly terminal TSA ensembles	36
D. Simulations and comparison with theory	38
VII. A model of cytokinetic ring constriction with distinct effective force laws	38
A. The fast turnover limit	40
B. Stalled turnover limits	41
C. Simulations	41
D. Path inference	42
VIII. Reverse-time ensemble path inference	42
A. Accounting for measurement noise	45
References	45

I. STOCHASTIC DYNAMICS SETTING

A. Markov processes

A time dependent stochastic process is defined by its probability density to be at its current position $\tilde{L}_n$ at time t_n and by the transitions it takes to get there starting at $\tilde{L}_0, t_0$. In this chapter $\tilde{L}$ denotes processes in forward time t . Formally such a process can be written as the transition probability density $P(\tilde{L}_n, t_n | \tilde{L}_{n-1}, t_{n-1}; \dots; \tilde{L}_0, t_0)$. For simplicity we assume that the current state of a stochastic process does only depend on its last step and not on its full history, i.e. that the process is memory free and obeys the Markov property

$$P(\tilde{L}_n, t_n | \tilde{L}_{n-1}, t_{n-1}; \dots; \tilde{L}_0, t_0) = P(\tilde{L}_n, t_n | \tilde{L}_{n-1}, t_{n-1}) . \quad (1)$$

The Markov property implies that the Chapman Kolmogorov equation

$$P(\tilde{L}_n, t_n | \tilde{L}_{n-2}, t_{n-2}) = \int d\tilde{L}_{n-1} P(\tilde{L}_n, t_n | \tilde{L}_{n-1}, t_{n-1}) P(\tilde{L}_{n-1}, t_{n-1} | \tilde{L}_{n-2}, t_{n-2}) \quad (2)$$

is fulfilled which we will use repeatedly in the subsequent derivations.

B. SDE and Fokker Planck representations

The evolution of a dynamical system under the influence of random forcing can often be studied using a Langevin equation

$$d\tilde{L}(t) = f(\tilde{L}) dt + \sqrt{D} dW_t . \quad (3)$$

The first term defines the deterministic drift $f(\tilde{L})$ the second the strength D of random fluctuations. Here the term dW_t denotes the Wiener process increment with zero mean $\langle dW_t \rangle = 0$ and delta correlated covariance $\langle dW_t dW_{t'} \rangle = D\delta(t - t')$. Throughout this text we adopt the Ito-interpretation of Eq. (3) which assures that the random forcing is always applied at the beginning of a discrete time interval dt .

Using Itos Lemma[1]

$$dg(\tilde{L}(t)) = \left(f(\tilde{L}) \frac{\partial g(\tilde{L})}{\partial \tilde{L}} + \frac{D}{2} \frac{\partial^2 g(\tilde{L})}{\partial \tilde{L}^2} \right) dt + \sqrt{D} \frac{\partial g(\tilde{L})}{\partial \tilde{L}} dW_t , \quad (4)$$

which shows how to apply a change of variables for quantities that are governed by Eq. (3), we can derive an evolution equation for its probability distribution $P(\tilde{L}, t | \tilde{L}_0, t_0)$. This evolution equation is called the (forward) Fokker-Planck equation (FPE) and is an equivalent description of the stochastic dynamics described in Eq. (3). A derivation can be found in Gardiner[1]. Averaging Eq. (4) with respect to $P(\tilde{L}, t | \tilde{L}_0, t_0)$, twice integrating by parts and identifying $g(\tilde{L})$ with a delta-function then leads to the evolution equation[1]. The resulting partial differential equation

$$\frac{\partial}{\partial t} P(\tilde{L}, t | \tilde{L}_0, t_0) = - \frac{\partial}{\partial \tilde{L}} f(\tilde{L}) P(\tilde{L}, t | \tilde{L}_0, t_0) + \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t | \tilde{L}_0, t_0) \quad (5)$$

is the sought (forward) Fokker-Planck equation. The adjoint equation is called the backward Fokker-Planck equation

$$\frac{\partial}{\partial t} P(\tilde{L}_f, t_f | \tilde{L}, t) = - f(\tilde{L}) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}_f, t_f | \tilde{L}, t) - \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}_f, t_f | \tilde{L}, t) . \quad (6)$$

and defines the evolution from a initial condition $\tilde{L}$ to a finale state $\tilde{L}_f$. It is important to note that after relabeling both equations yield the same transition probabilities and that it is only a different perspective to solve the same problem. The term 'backward'-Fokker-Planck equation is somewhat ill-posed and can not be exchanged for 'time-reversed'. In analogy to quantum mechanics, the forward Fokker-Planck equation describes the time evolution of the probability density and an average of any dynamical property is taken at a specific time point t like in the Schrödinger picture. Conversely, the backward Fokker-Planck equation corresponds to the Heisenberg picture where the focus lies on the time evolution of a dynamical observable and the averages are taken over initial conditions. Like in quantum mechanics both approaches are thus describing exactly the same physics. They are merely offering different perspectives and can be interchanged by a simple transformation. Ultimately both approaches hence refer to the same transition probability densities. In the next section we show how the concept of time-reversal is to be introduced into a stochastic framework.

II. TIME REVERSAL AND ALIGNMENT

The mathematical construction of the aligned and time reversed ensemble can be split into three parts. (i) The general definition of time reversal for SDEs, (ii) its adaptation to sample paths $\tilde{L}_i(t)$ that hit a target state $\tilde{L}_{\text{TS}}$ after time T_i , and (iii) the alignment and time reversal of a complete ensemble of sample paths $L_i(\tau)$ into one ensemble depending on their “time to completion” $\tau = T_i - t$.

In the first part we present the SDE for the time reversal of sample paths $\tilde{L}_i(t)$ of fixed lifetime T . The ensemble $P(\tilde{L}, t)$ of sample paths $\tilde{L}_i(t)$, evolves freely according to a general stochastic law of motion. The reverse time ensemble then consists of sample paths $L_i(\tau) = \tilde{L}_i(T - \tau)$. All sample paths $\tilde{L}_i(t)$ start at the same time t_0 and evolve for the same time interval T . The time reversed SDE describes precisely this ensemble, but in reverse time. It starts from the final distribution of the forward process $P(L, \tau_0) = P(\tilde{L}, T)$ and evolves into the initial distribution $P(L, T) = P(\tilde{L}, t_0)$. One illustrative example realization of both a forward ensemble $P(\tilde{L}, t)$ and time reversed ensemble $P(L, \tau)$ is shown in Fig. 1.

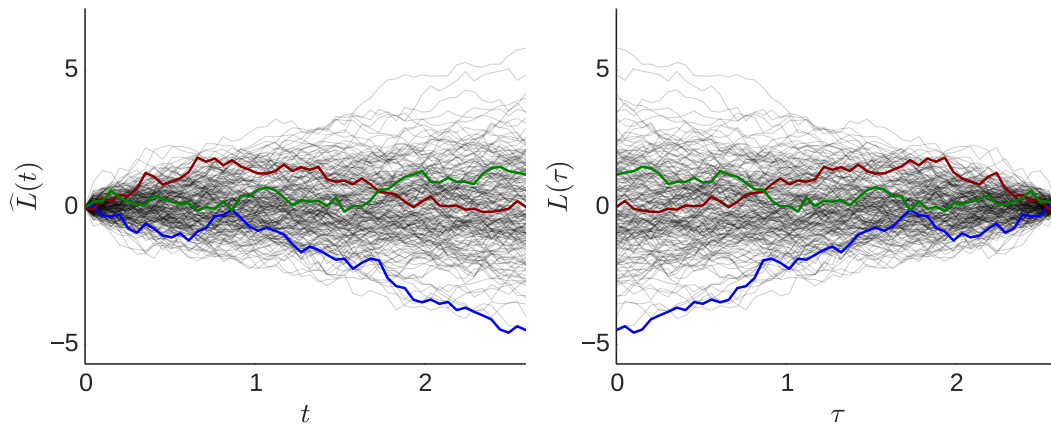


FIG. 1. **Time reversal of an ensemble with natural boundary conditions.** (Left): Evolution of a set of sample paths $\tilde{L}_i(t)$ up to a time T . (Right): The set of time reverted sample paths $L_i(\tau)$. Natural boundary conditions are defined as $P(\tilde{L} \rightarrow \pm\infty, t) = 0$.

In the second part, we consider the time reversal of sample paths $\tilde{L}_i(t)$ that hit a target state $\tilde{L}_{\text{TS}}$ after a fixed time $T_i = T$. In this step, we pick precisely those sample paths L_i of the full forward ensemble $P(\tilde{L}, t)$ that arrive at a target state after a particular time to completion T_i . The time reversed SDE for this sub-ensemble is the same as derived in the first part, with the initial condition of the reverse time process specialized as a delta-distribution $P(L, \tau_0) = \delta(\tilde{L} - \tilde{L}_{\text{TS}})$ localized at the target state. All sample paths of this sub-ensemble start at $\tilde{L}_{\text{TS}}$ and progress towards the initial conditions of the forward process. They are all of the same lifetime T_i . A realization of this time reversed sub-ensemble together with the full forward ensemble up to time T_i is shown in Fig. 2.

Finally, in the last step, we construct the complete ensemble of time reversed TSA sample paths $L_i(\tau)$, of different lifetimes T_i , in a common time to completion reference frame. Depending on its noise and underlying stochastic law of motion each sample path $\tilde{L}_i(t)$ hits $\tilde{L}_{\text{TS}}$ after a different time T_i , which by itself is a random variable. The distribution $\rho_{\tilde{L}_{\text{TS}}}(T|\tilde{L}_0)$ of lifetimes T is defined by the forward SDE of Eq. (3) and its initial conditions. To obtain the complete time reversed ensemble, we first construct a time reversed sub-ensemble for each lifetime T_i . The complete time reversed ensemble is then obtained by averaging over these sub-ensembles with respect to the distribution of lifetimes $\rho_{\tilde{L}_{\text{TS}}}(T|\tilde{L}_0)$. This construction of the complete time reversed ensemble out of sub-ensembles of different lifetimes is demonstrated in Fig. 3. Target state alignment is achieved by constructing each time reversed sub-ensemble starting from $\tilde{L}_{\text{TS}}$ and $\tau = 0$. The full time reversed ensemble then also starts from this initial state $(\tilde{L}_{\text{TS}}, \tau = 0)$.

The following sections give a mathematically detailed account of the three steps leading to the construction of an target state aligned and time reversed ensemble. We start with the derivation of a general time reversed SDE.

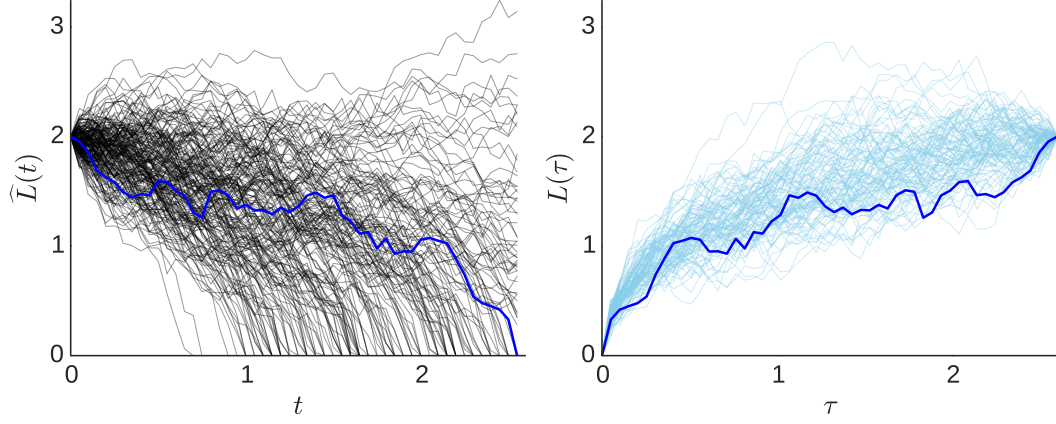


FIG. 2. **Time reversal of a terminating sub-ensemble.** (Left): Evolution of a set of sample paths $\tilde{L}_i(t)$ up to an irreversible target state. Different sample paths $\tilde{L}_i(t)$ hit $\tilde{L}_{TS}$ at different times T_i . (Right): Time reversal of a representative sample path $\tilde{L}_i(t)$ that has hit $\tilde{L}_{TS}$ after time T_i (dark blue). A realization of the sub-ensemble that has terminated after T_i (light blue).

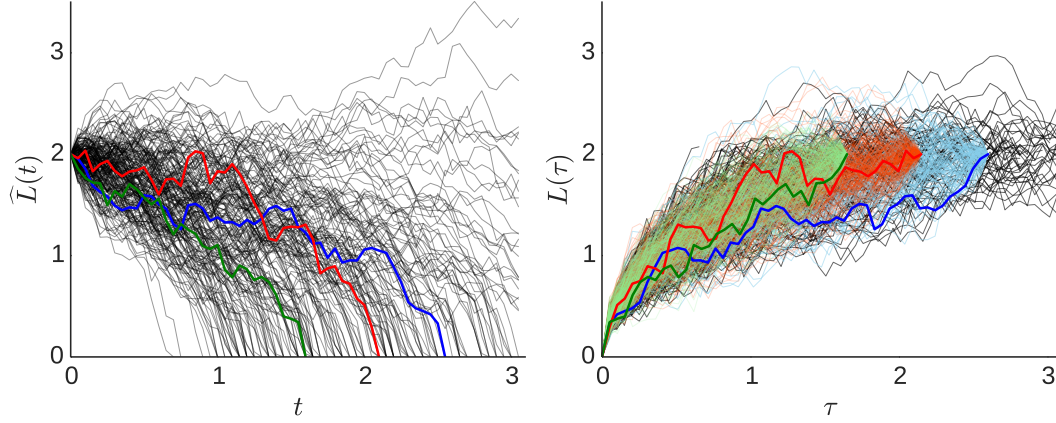


FIG. 3. **Time reversal and alignment of the complete terminating ensemble.** (Left): A set of realizations of the complete forward ensemble. Three exemplary sample paths of different lifetimes T_i are highlighted. (Right): Time reversal of terminating sub-ensembles according to their lifetime T_i . The full ensemble is formed of sub-ensembles where three are exemplary highlighted.

A. The reverse time Fokker-Planck equation

Time reversal of a stochastic process is a non trivial operation. While a deterministic process is described by an ODE and a single final condition, time reversal of a stochastic process does not simply turn a forward SDE into a reverse time SDE. This finding is rooted in the observation that transition probability densities of the reverse process must depend both on the initial and final conditions of the forward process. We start by noting that a stochastic process constrained by initial and final conditions can be constructed from the product of two transition probability densities

$$P(\tilde{L}_f, t_f | \tilde{L}, t) P(\tilde{L}, t | \tilde{L}_0, t_0). \quad (7)$$

To ensure that sample paths start at $(\tilde{L}_0, t_0)$ and end at $(\tilde{L}_f, t_f)$ with probability one, this process is normalized using the Chapman Kolmogorov Eq. (2). The normalized process

$$P(\tilde{L}, t | \tilde{L}_f, t_f; \tilde{L}_0, t_0) = \frac{P(\tilde{L}_f, t_f | \tilde{L}, t) P(\tilde{L}, t | \tilde{L}_0, t_0)}{P(\tilde{L}_f, t_f | \tilde{L}_0, t_0)} \quad (8)$$

is called a bridge process of lifetime $T = t_f - t_0$ and defines the evolution of stochastic processes conditioned on both the initial $(\tilde{L}_0, t_0)$ and final conditions $(\tilde{L}_f, t_f)$ [2]. We note that $P(\tilde{L}, t | \tilde{L}_f, t_f; \tilde{L}_0, t_0)$ is symmetric under time reversal i.e. relabeling of indices. The initial conditions of the forward process $(\tilde{L}_0, t_0)$ are then the final conditions of the reverse time process (L_f, τ_f) and vice versa. The bridge process defined in reverse time $\tau = t_f - t$ and with $\tau_0 = 0$ then reads $P(L, \tau | L_0, \tau_0, L_f, \tau_f)$. The SDE that describes this process is known [3] and assumes the form

$$dL(\tau) = \left(-f(L) + D \frac{\partial}{\partial L} \log (P^{\text{fw}}(L, T - \tau | L_f, 0)) \right) d\tau + \sqrt{D} dW_\tau \quad (9)$$

where $P^{\text{fw}}(L, T - \tau | L_f, 0)$ denotes the solution of the forward Fokker Planck equation evaluated in reverse time τ . The initial conditions of this process are given by the final distribution $P^{\text{fw}}(\tilde{L}_f, t_f | \tilde{L}_0, t_0)$ of the forward process. The guiding force $D \frac{\partial}{\partial L} \log P^{\text{fw}}(L, T - \tau | L_f, 0)$ ensures that every $L_i(\tau)$ synthesized in reverse time τ is statistically indistinguishable from a forward sample path $\tilde{L}_i$ of lifetime T . Close to $\tau \approx T$, $P^{\text{fw}}(L, T - \tau | L_f, 0)$ becomes peaked and deviations from $P(\tilde{L}_0) = \delta(\tilde{L} - \tilde{L}_0)$ are suppressed by strong gradients of the guiding potential. The system is driven towards the initial conditions of the forward process. Note that the guiding force takes the form of an entropic force[4] which reverses the single trajectory entropy production of the forward process[5] until the entropy of the forward initial conditions is reinstalled. An illustration of both an example forward ensemble and its time reversed equivalent is shown in Fig. 1.

The SDE Eq. (9) captures the dynamics of a time reversed process of fixed lifetime T and is the first key equation to our approach. Its original derivation[3] builds on the equivalence of Langevin and Fokker-Planck equations in which Eq. (9) is obtained from the reverse time Fokker-Planck Equation

$$\begin{aligned} \frac{\partial P(L, \tau | L_f, \tau_f; L_0, \tau_0)}{\partial \tau} &= \frac{\partial}{\partial L} \left[\left(f(L) - D \frac{\partial}{\partial L} \log P^{\text{fw}}(L, T - \tau | L_f, 0) \right) P(L, \tau | L_f, \tau_f; L_0, \tau_0) \right] \\ &+ \frac{D}{2} \frac{\partial^2}{\partial L^2} P(L, \tau | L_f, \tau_f; L_0, \tau_0) . \end{aligned} \quad (10)$$

The conditional probability density $P(L, \tau | L_f, \tau_f; L_0, \tau_0)$ describes the evolution of reverse sample paths $L(\tau)$ of fixed lifetime T . It depends on both, the initial and final conditions $\tilde{L}_0$ and $\tilde{L}_f$ of the forward process. The subsequent derivation of Eq. (10) follows Anderson's[3]. We here use the notation employed in the main text and add intermediate steps omitted in Anderson[3]. A mathematically more rigorous derivation can be found in Föllmer[6].

The derivation proceeds in three steps: First, we derive an evolution equation of the joint probability density $P(\tilde{L}, t; \tilde{L}_f, t_f | \tilde{L}_0, t_0)$ using both the backward and forward Fokker-Planck equation Eq. (6) and Eq. (5) for the forward sample paths $\tilde{L}(t)$ that evolve with time t . From this intermediate result the evolution equation for the conditional probability density $P(\tilde{L}, t | \tilde{L}_f, t_f; \tilde{L}_0, t_0)$ follows directly. It describes sample paths $\tilde{L}_i(t)$ that are constrained to both initial and final conditions. Finally we transform the evolution equation of $P(\tilde{L}, t | \tilde{L}_f, t_f; \tilde{L}_0, t_0)$ into the reverse time Fokker-Planck Equation for $P(L, \tau | L_f, \tau_f; L_0, \tau_0)$ by time reversal. Note, that we will omit writing out the explicit dependence on the initial conditions $(\tilde{L}_0, t_0)$ during this derivation for notational clarity. Even if not stated, every probability density used in this derivation carries $(\tilde{L}_0, t_0)$ as a condition.

We start with writing the joint probability density from Eq. (7)

$$P(\tilde{L}, t; \tilde{L}_f, t_f) = P(\tilde{L}_f, t_f | \tilde{L}, t) P(\tilde{L}, t) \quad (11)$$

as a product of a conditional probability densities assuming $t_f \geq t$. Taking the derivative with respect to t on both sides and multiplying both sides with (-1) , we obtain

$$-\frac{\partial P(\tilde{L}, t; \tilde{L}_f, t_f)}{\partial t} = -P(\tilde{L}, t) \frac{\partial}{\partial t} P(\tilde{L}_f, t_f | \tilde{L}, t) - P(\tilde{L}_f, t_f | \tilde{L}, t) \frac{\partial}{\partial t} P(\tilde{L}, t) \quad (12)$$

Substituting $\frac{\partial}{\partial t} P(\tilde{L}_f, t_f | \tilde{L}, t)$ using the backward Fokker-Planck Eq. (6) and $\frac{\partial}{\partial t} P(\tilde{L}, t)$ using the forward Fokker-Planck Eq. (5) yields

$$\begin{aligned} -\frac{\partial P(\tilde{L}, t; \tilde{L}_f, t_f)}{\partial t} &= P(\tilde{L}, t) \left[f(\tilde{L}) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}_f, t_f | \tilde{L}, t) + \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}_f, t_f | \tilde{L}, t) \right] \\ &+ P(\tilde{L}_f, t_f | \tilde{L}, t) \left[\frac{\partial}{\partial \tilde{L}} f(\tilde{L}) P(\tilde{L}, t) - \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t) \right] . \end{aligned} \quad (13)$$

In the next steps we rewrite all D -dependent terms to eventually obtain a diffusion term of the form $\frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t; \tilde{L}_f, t_f)$ and a residual term. We start by applying the product rule to all D -dependent terms in Eq. (13) and find

$$\begin{aligned} & \frac{D}{2} \left[P(\tilde{L}, t) \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}_f, t_f | \tilde{L}, t) \right] - \frac{D}{2} \left[P(\tilde{L}_f, t_f | \tilde{L}, t) \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t) \right] = \\ & = \frac{D}{2} \left[\frac{\partial}{\partial \tilde{L}} \left(P(\tilde{L}, t) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}_f, t_f | \tilde{L}, t) \right) - \left(\frac{\partial}{\partial \tilde{L}} P(\tilde{L}, t) \right) \left(\frac{\partial}{\partial \tilde{L}} P(\tilde{L}_f, t_f | \tilde{L}, t) \right) \right] \\ & - \frac{D}{2} \left[\frac{\partial}{\partial \tilde{L}} \left(P(\tilde{L}_f, t_f | \tilde{L}, t) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}, t) \right) - \left(\frac{\partial}{\partial \tilde{L}} P(\tilde{L}_f, t_f | \tilde{L}, t) \right) \left(\frac{\partial}{\partial \tilde{L}} P(\tilde{L}, t) \right) \right]. \end{aligned} \quad (14)$$

The product terms cancel and the equation simplifies to

$$= \frac{D}{2} \frac{\partial}{\partial \tilde{L}} \left(P(\tilde{L}, t) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}_f, t_f | \tilde{L}, t) - P(\tilde{L}_f, t_f | \tilde{L}, t) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}, t) \right). \quad (15)$$

Using the product rule a second time, but now only for the first term

$$= \frac{D}{2} \frac{\partial}{\partial \tilde{L}} \left(\frac{\partial}{\partial \tilde{L}} \left(P(\tilde{L}, t) P(\tilde{L}_f, t_f | \tilde{L}, t) \right) - P(\tilde{L}_f, t_f | \tilde{L}, t) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}, t) - P(\tilde{L}_f, t_f | \tilde{L}, t) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}, t) \right), \quad (16)$$

and summing identical terms, yields the described diffusion term minus a residual term

$$= \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} \left(P(\tilde{L}, t) P(\tilde{L}_f, t_f | \tilde{L}, t) \right) - D \frac{\partial}{\partial \tilde{L}} \left(P(\tilde{L}_f, t_f | \tilde{L}, t) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}, t) \right). \quad (17)$$

Next we consider all $f(\tilde{L})$ containing terms in Eq. (13). Application of the product rule allows to simplify terms to obtain

$$\begin{aligned} P(\tilde{L}, t) f(\tilde{L}) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}_f, t_f | \tilde{L}, t) + P(\tilde{L}_f, t_f | \tilde{L}, t) \frac{\partial}{\partial \tilde{L}} f(\tilde{L}) P(\tilde{L}, t) = \\ = \frac{\partial}{\partial \tilde{L}} \left(f(\tilde{L}) P(\tilde{L}_f, t_f | \tilde{L}, t) P(\tilde{L}, t) \right). \end{aligned} \quad (18)$$

We can now collect all rewritten $f(\tilde{L})$ and D -dependent terms and (after joining the probability densities $P(\tilde{L}_f, t_f | \tilde{L}, t)$ and $P(\tilde{L}, t)$ using Eq. (11)) bring Eq. (13) into the form

$$\begin{aligned} -\frac{\partial P(\tilde{L}, t; \tilde{L}_f, t_f)}{\partial t} &= \frac{\partial}{\partial \tilde{L}} \left[f(\tilde{L}) P(\tilde{L}, t; \tilde{L}_f, t_f) - D P(\tilde{L}_f, t_f | \tilde{L}, t) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}, t) \right] \\ &+ \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t; \tilde{L}_f, t_f). \end{aligned} \quad (19)$$

Note that the term $-D P(\tilde{L}_f, t_f | \tilde{L}, t) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}, t)$, although depending on the diffusion constant D , is now assigned to the drift part. Rewriting this term, using again Eq. (11) in the form $P(\tilde{L}_f, t_f | \tilde{L}, t) = P(\tilde{L}_f, t_f; \tilde{L}, t) / P(\tilde{L}, t)$, yields

$$\begin{aligned} -\frac{\partial P(\tilde{L}, t; \tilde{L}_f, t_f)}{\partial t} &= \frac{\partial}{\partial \tilde{L}} \left[\left(f(\tilde{L}) - \frac{D}{P(\tilde{L}, t)} \frac{\partial P(\tilde{L}, t)}{\partial \tilde{L}} \right) P(\tilde{L}, t; \tilde{L}_f, t_f) \right] \\ &+ \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t; \tilde{L}_f, t_f). \end{aligned} \quad (20)$$

This is our first intermediate result. The evolution equation for the joined probability density $P(\tilde{L}, t; \tilde{L}_f, t_f)$.

Dividing this equation by $P(\tilde{L}_f, t_f)$, the distribution of the final state, results in an evolution equation of the form

$$\begin{aligned} -\frac{\partial P(\tilde{L}, t | \tilde{L}_f, t_f)}{\partial t} &= \frac{\partial}{\partial \tilde{L}} \left[\left(f(\tilde{L}) - \frac{D}{P(\tilde{L}, t)} \frac{\partial P(\tilde{L}, t)}{\partial \tilde{L}} \right) P(\tilde{L}, t | \tilde{L}_f, t_f) \right] \\ &+ \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t | \tilde{L}_f, t_f), \end{aligned} \quad (21)$$

which in its force term can be simplified further to obtain

$$-\frac{\partial P(\tilde{L}, t|\tilde{L}_f, t_f)}{\partial t} = \frac{\partial}{\partial \tilde{L}} \left[\left(f(\tilde{L}) - D \frac{\partial}{\partial \tilde{L}} \log P(\tilde{L}, t) \right) P(\tilde{L}, t|\tilde{L}_f, t_f) \right] + \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t|\tilde{L}_f, t_f) . \quad (22)$$

To make the interpretation of this equation and especially of the term $P(\tilde{L}, t)$ explicit, the dependence of every probability density on the initial conditions $(\tilde{L}_0, t_0)$, suppressed throughout this derivation, is now restored to yield

$$-\frac{\partial P(\tilde{L}, t|\tilde{L}_0, t_0; \tilde{L}_f, t_f)}{\partial t} = \frac{\partial}{\partial \tilde{L}} \left[\left(f(\tilde{L}) - D \frac{\partial}{\partial \tilde{L}} \log P(\tilde{L}, t|\tilde{L}_0, t_0) \right) P(\tilde{L}, t|\tilde{L}_0, t_0; \tilde{L}_f, t_f) \right] + \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t|\tilde{L}_0, t_0; \tilde{L}_f, t_f) . \quad (23)$$

The conditional probability density $P(\tilde{L}, t|\tilde{L}_0, t_0; \tilde{L}_f, t_f)$ describes the evolution of sample paths $\tilde{L}(t)$ in wall time t connecting an initial state $\tilde{L}_0, t_0$ with a final state $\tilde{L}_f, t_f$. This is our second intermediate result.

The time reversed Fokker-Planck Equation can be obtained from Eq. (23) by replacing the wall time t with the reverse time τ . Setting $\tau = t_f - t$, and the duration of the forward process after which it is reverted to $T = t_f - t_0$, the resulting equation reads

$$\frac{\partial P(L, \tau|\tilde{L}_0, t_0, \tilde{L}_f, t_f)}{\partial \tau} = \frac{\partial}{\partial L} \left[\left(f(L) - D \frac{\partial}{\partial L} \log P^{\text{fw}}(L, T - \tau|L_f, 0) \right) P(L, \tau|\tilde{L}_0, t_0, \tilde{L}_f, t_f) \right] + \frac{D}{2} \frac{\partial^2}{\partial L^2} P(L, \tau|\tilde{L}_0, t_0, \tilde{L}_f, t_f) . \quad (24)$$

The superscript (fw) was added for clarity. In the final step we replace all forward coordinates $\tilde{L}$ by their time reversed equivalent L and obtain the final result already stated in Eq. (10). The initial conditions of Eq. (10) can be drawn from the final distribution of the forward process $P^{\text{fw}}(\tilde{L}_f, t_f|\tilde{L}_0, t_0)$. Solving or approximating the time reversed Fokker-Planck Equation therefore crucially depends on knowledge about the forward process.

B. The time reversal of a terminating sub-ensemble

Time reversal of a sub-ensemble which ends at a target state $\tilde{L}_{\text{TS}}$ after time $T = t_f - t_0$ is a special case of the general formulation of the reverse time Fokker-Planck Eq. (10). From a constructive perspective two specifications are necessary. First, to invoke an irreversible target state, an absorbing boundary condition

$$P(\tilde{L}, t|\tilde{L}_0, t_0) = 0 \quad \text{for} \quad \tilde{L} = \tilde{L}_{\text{TS}} \quad (25)$$

must be implemented. Second, with absorbing boundary conditions the product of the two transition probability densities which define the not yet normalized bridge Eq. (7), is zero for $\tilde{L}_f \rightarrow \tilde{L}_{\text{TS}}$. The second transition $P(\tilde{L}_f, t_f|\tilde{L}, t)$ in Eq. (7) must therefore be replaced by the probability to reach the target state $\tilde{L}_{\text{TS}}$ starting from $\tilde{L}$ and after a time $t_f - t$. This probability flux into the boundary is called a hitting time distribution and is defined as

$$\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) = -\frac{\partial}{\partial t_f} \int_{\tilde{L}_{\text{TS}}}^{\infty} dL_f P(\tilde{L}_f, t_f|\tilde{L}, t) . \quad (26)$$

The un-normalized bridge, which starts at $\tilde{L}_0$, ends at $\tilde{L}_f = \tilde{L}_{\text{TS}}$ and only includes sample paths which reach the target state exactly after a time $T = t_f - t_0$, is then defined as

$$\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t_0) . \quad (27)$$

To ensure that sample paths starting at $\tilde{L}_0$ end at $\tilde{L}_f = \tilde{L}_{\text{TS}}$ with probability one, Eq. (27) is normalized with respect to the hitting time distribution $\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}_0, t_0)$. The full bridge ending at a target state then reads

$$R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t|\tilde{L}_0, t_0; t_f) := \frac{\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t_0)}{\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}_0, t_0)} . \quad (28)$$

We will show below, that $\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t)$ is a solution of the backward Fokker Planck and that the normalization of this bridge process is again a hitting time distribution. The dynamics of Eq. (28) written in reverse time τ are therefore formally identical to Eq. (10) and read

$$\begin{aligned} \frac{\partial R_{L_{\text{TS}}}(L, \tau|L_f, \tau_f; \tau_0)}{\partial \tau} &= \frac{\partial}{\partial L} \left[\left(f(L) - D \frac{\partial}{\partial L} \log P^{\text{fw}}(L, T - \tau|L_f, 0) \right) R_{L_{\text{TS}}}(L, \tau|L_f, \tau_f; \tau_0) \right] \\ &+ \frac{D}{2} \frac{\partial^2}{\partial L^2} R_{L_{\text{TS}}}(L, \tau|L_f, \tau_f; \tau_0) . \end{aligned} \quad (29)$$

We again added the upper index (fw) for clarity. The corresponding reverse time SDE is thus identical to Eq. (9) with $P^{\text{fw}}(L, T - \tau|\tilde{L}_0, 0)$ assumed with an absorbing boundary at L_{TS} . Assuming absorbing boundary conditions for $P^{\text{fw}}(\tilde{L}, t|\tilde{L}_0, t_0)$, the guiding force in Eq. (9) automatically prevents time reversed sample paths $L_i(\tau)$ from returning to $\tilde{L}_{\text{TS}}$ for $\tau > 0$. This can be seen by evaluating the guiding force $D \frac{\partial}{\partial L} \log P^{\text{fw}}(L, T - \tau|L_f, 0)$ with respect to the absorbing boundary condition. Lets assume the irreversible target state $\tilde{L}_{\text{TS}}$ is a lower boundary of the one dimensional dynamic. As $P^{\text{fw}}(L, T - \tau|L_f, 0) \xrightarrow{L \rightarrow \tilde{L}_{\text{TS}}} 0$ approaches zero from above close to the absorbing boundary, $\log P^{\text{fw}}(L, T - \tau|L_f, 0) \xrightarrow{L \rightarrow \tilde{L}_{\text{TS}}} -\infty$ diverges. The guiding force $D \frac{\partial}{\partial L} \log P^{\text{fw}}(L, T - \tau|L_f, 0) \xrightarrow{L \rightarrow \tilde{L}_{\text{TS}}} \infty$ therefore diverges as well and thus behaves as an infinitely large barrier that prevents all $L_i(\tau)$ from returning to $\tilde{L}_{\text{TS}}$.

1. The target state bridge normalization

In this sub section we show that $\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}_0, t_0)$ is the normalization for the target-state bridge process. One step in this calculation is based on the assumption that the Chapman-Kolmogorov equation Eq. (2) also holds, when not the full probability space is considered but only those transitions which do not end at a target state, i.e. $P(\tilde{L}', t'|\tilde{L}, t)$. This assumption is implicit to all calculations of Fokker-Planck equations with absorbing boundary conditions imposed. Nevertheless, as we are not aware of an explicit demonstration of this claim, we will briefly sketch a derivation below. This sub-section first shows that a Chapman Kolmogorov equation also holds for this subspace of transitions. In a second step this result is used to determine the normalization of a bridge process with target state at an absorbing boundary.

We first demonstrate that a Chapman-Kolmogorov like equation also holds for $P(\tilde{L}, t|\tilde{L}_0, t_0)$ and $P(\tilde{L}_f, t_f|\tilde{L}, t)$ which are not normalized, as transitions to the absorbing boundary are split off as an extra term. Splitting the expression into those two terms yields

$$P^{\text{full}}(\tilde{L}, t|\tilde{L}_0, t_0) = \delta(\tilde{L} - \tilde{L}_{\text{TS}}) P^{\text{TS}}(t|\tilde{L}_0, t_0) + P(\tilde{L}, t|\tilde{L}_0, t_0) , \quad (30)$$

where $P^{\text{TS}}(t|\tilde{L}_0, t_0)$ denotes the over time $t - t_0$ at the target state accumulated probability mass. For this normalized expression Chapman-Kolmogorov holds

$$P^{\text{full}}(\tilde{L}_f, t_f|\tilde{L}_0, t_0) = \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L} P^{\text{full}}(\tilde{L}_f, t_f|\tilde{L}, t) P^{\text{full}}(\tilde{L}, t|\tilde{L}_0, t_0) \quad (31)$$

and can be rewritten using the definition Eq. (30) to yield

$$= \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L} \left(\delta(\tilde{L}_f - \tilde{L}_{\text{TS}}) P^{\text{TS}}(t_f|\tilde{L}, t) + P(\tilde{L}_f, t_f|\tilde{L}, t) \right) P^{\text{full}}(\tilde{L}, t|\tilde{L}_0, t_0) . \quad (32)$$

Evaluating the first term of the product we find

$$= \delta(\tilde{L}_f - \tilde{L}_{\text{TS}}) P^{\text{TS}}(t_f|\tilde{L}_0, t_0) + \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L} P(\tilde{L}_f, t_f|\tilde{L}, t) P^{\text{full}}(\tilde{L}, t|\tilde{L}_0, t_0) . \quad (33)$$

Due to the absorbing boundary condition, transitions from $\tilde{L}_0 \rightarrow \tilde{L} \rightarrow \tilde{L}_f$, with $\tilde{L}_f \neq \tilde{L}_{\text{TS}}$, are only possible if the intermediate step does not end at the absorbing boundary. We can therefore simplify the remaining integral to include only transitions that do not end at the target state. The final equation reads

$$= \delta(\tilde{L}_f - \tilde{L}_{\text{TS}}) P^{\text{TS}}(t_f|\tilde{L}_0, t_0) + \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L} P(\tilde{L}_f, t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t_0) . \quad (34)$$

Comparing this result with the definition of $P^{\text{full}}(\tilde{L}_f, t_f | \tilde{L}, t)$ in Eq. (30), this implies, that the Chapman Kolmogorov like identity

$$P(\tilde{L}_f, t_f | \tilde{L}_0, t_0) = \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L} P(\tilde{L}_f, t_f | \tilde{L}, t) P(\tilde{L}, t | \tilde{L}_0, t_0) \quad (35)$$

holds. We next use this identity to obtain the normalization for the target-state bridge Eq. (27) by integration over $\tilde{L}$. Using the definition of the hitting time distribution

$$\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L} \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) P(\tilde{L}, t | \tilde{L}_0, t_0) = - \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L} P(\tilde{L}, t | \tilde{L}_0, t_0) \frac{\partial}{\partial t_f} \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_f P(\tilde{L}_f, t_f | \tilde{L}, t), \quad (36)$$

taking both the derivative with respect to t_f and the integral with respect to $\tilde{L}_f$ to the outside, we arrive at

$$= - \frac{\partial}{\partial t_f} \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_f \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L} P(\tilde{L}, t | \tilde{L}_0, t_0) P(\tilde{L}_f, t_f | \tilde{L}, t). \quad (37)$$

We replace the inner integral by the above derived version of the Chapman Kolmogorov equation Eq. (35)

$$= - \frac{\partial}{\partial t_f} \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_f P(\tilde{L}_f, t_f | \tilde{L}_0, t_0) \quad (38)$$

and find that the hitting time distribution

$$= \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}_0, t_0) \quad (39)$$

for processes starting at $(\tilde{L}_0, t_0)$ and ending at $(\tilde{L}_{\text{TS}}, t_f)$ is the normalization of the bridge process Eq. (28).

2. Backward Fokker-Planck for hitting time distribution

To conclude the above section on bridge processes with target states we recall that the hitting time distribution $\rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t)$ fulfills the backward Fokker-Planck equation Eq. (6). This can be seen by taking the derivative of Eq. (26) with respect to t

$$\frac{\partial}{\partial t} \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) = - \frac{\partial}{\partial t_f} \int_{\tilde{L}_{\text{TS}}}^{\infty} dL_f \frac{\partial}{\partial t} P(\tilde{L}_f, t_f | \tilde{L}, t). \quad (40)$$

Substituting the backward Fokker-Planck equation Eq. (6)

$$= - \frac{\partial}{\partial t_f} \int_{\tilde{L}_{\text{TS}}}^{\infty} dL_f \left(-f(\tilde{L}) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}_f, t_f | \tilde{L}, t) - \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}_f, t_f | \tilde{L}, t) \right)$$

and replacing all $P(\tilde{L}_f, t_f | \tilde{L}, t)$ dependent terms by the definition of the hitting time distribution Eq. (26), we obtain the backward Fokker Planck for hitting time distributions

$$= -f(\tilde{L}) \frac{\partial}{\partial \tilde{L}} \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) - \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t). \quad (41)$$

C. The time reversal and alignment of the full terminating ensemble

So far we considered the time reversal of sample paths $\tilde{L}_i(t)$ of identical lifetime $T_i = T$. The lifetime T_i , however, is a stochastic variable. Different sample paths $\tilde{L}_i(t)$ reach the target state after different lifetimes T_i . The distribution of lifetimes is the hitting time distribution $\rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}_0, t_0)$. The full forward ensemble of all sample paths starting at $(\tilde{L}_0, t_0)$ and ending at $\tilde{L}_{\text{TS}}$ after a random time t_f can therefore be understood as comprised of sub-ensembles

$R_{L_{\text{TS}}}(\tilde{L}, t | \tilde{L}_0, t_0; t_f)$ each of a different lifetime T_i . Each of these sub-ensembles then contributes to the full ensemble with a weight given by the hitting time distribution $\rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}_0, t_0)$

In this perspective, target state alignment consists of detaching all these sub-ensembles from their initiation point $(\tilde{L}_0, t_0)$ and shifting all sample paths to reach the target state at a common reference time t_f . The resulting target state aligned ensemble in forward time

$$R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f | \tilde{L}_0) = \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}_0, t_0) R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t | \tilde{L}_0, t_0; t_f) \quad (42)$$

is then given as the hitting time weighted integral of target-state aligned sub-ensembles. By target state alignment we choose one t_f for all sub-ensembles. Keeping t_f fixed, $T_i = t_f - t_0$ or respectively t_0 becomes the random variable over which we integrate. Notably, not all sub-ensembles contribute to the full TSA ensemble at all times. The longer the lifetime $t_f - t$, the fewer sub-ensembles have a lifetime T_i long enough to still contribute. The integral bounds therefore enforce that at time t only those sub-ensembles with a minimal lifetime $t_f - t$ contribute.

In reverse time τ the expression for the TSA ensemble is

$$R_{L_{\text{TS}}}(L, \tau; \tau_0 | L_f) = \int_{\tau}^{\infty} d\tau_f \rho_{L_{\text{TS}}}(\tau_0 | L_f, \tau_f) R_{L_{\text{TS}}}(L, \tau | L_f, \tau_f; \tau_0) . \quad (43)$$

With τ_0 identically fixed for all sub-ensembles only those sub-ensembles contribute at time τ with a lifetime $T_i \geq \tau - \tau_0$. The reverse time TSA ensemble $R_{L_{\text{TS}}}(L, \tau; \tau_0 | L_f)$ is therefore not normalized. It decays with the the hitting time distribution $\rho_{L_{\text{TS}}}(\tau_0 | L_f, \tau_f)$.

In the next step we generalize this expression to include sample-paths with their initial position $\tilde{L}_0$ drawn from an input distributions $P^{\text{in}}(\tilde{L}_0)$. For the reverse time TSA ensemble this generalization simply amounts to integrating over Eq. (43) with respect to $P^{\text{in}}(L_f)$ and we arrive at

$$R_{L_{\text{TS}}}(L, \tau; \tau_0) = \int_{L_{\text{TS}}}^{\infty} dL_f P^{\text{in}}(L_f) \int_{\tau}^{\infty} d\tau_f \rho_{L_{\text{TS}}}(\tau_0 | L_f, \tau_f) R_{L_{\text{TS}}}(L, \tau | L_f, \tau_f; \tau_0) . \quad (44)$$

This expression is exactly the same as stated in the main text, where the concept of TSA ensembles is introduced. There, we set $R(L, \tau) := R_{L_{\text{TS}}}(L, \tau; \tau_0)$ and neglected the for the intuition irrelevant dependency on L_{TS} and τ_0 .

Independent of its notation, $R_{L_{\text{TS}}}(L, \tau; \tau_0)$ satisfies an easy to interpret reverse time Fokker-Planck equation which reads

$$\begin{aligned} \frac{\partial}{\partial \tau} R_{L_{\text{TS}}}(L, \tau; \tau_0) &= -P^{\text{in}}(L) \rho_{L_{\text{TS}}}(\tau | L) \\ &- \frac{\partial}{\partial L} \left(\left[f(L) + D \frac{\partial}{\partial L} \log \left(\int_{L_{\text{TS}}}^L dL' e^{-\int^{L'} \frac{2f(L'')}{D} dL''} \left(1 - \int_{L_{\text{TS}}}^{L'} P^{\text{in}}(L'') dL'' \right) \right) \right] R_{L_{\text{TS}}}(L, \tau; \tau_0) \right) \\ &+ \frac{D}{2} \frac{\partial^2}{\partial L^2} R_{L_{\text{TS}}}(L, \tau; \tau_0) . \end{aligned} \quad (45)$$

The exact derivation is presented further below in this section. The first term constitutes a sink where probability mass proportional to the hitting time distribution is lost. For delta initial conditions $P^{\text{in}}(L) = \delta(L - L_f)$ the sink is only active for $L = L_f$. For arbitrary input distributions $P^{\text{in}}(L_f)$ the rate of probability loss is still proportional to the hitting time distribution but now additionally to the number of sample paths which originated in an interval $P^{\text{in}}(L) dL$. This is exactly in accordance with the construction of $R_{L_{\text{TS}}}(L, \tau; \tau_0)$ in Eq. (44). The second line represents the drift and the third a simple diffusion term.

This form of the Fokker Planck equation for the reverse time TSA ensemble Eq. (45) corresponds to the Langevin equation

$$dL(\tau) = \left(f(L) + D \frac{\partial}{\partial L} \log \left(\int_{L_{\text{TS}}}^L dL' e^{-\int^{L'} \frac{2f(L'')}{D} dL''} \left(1 - \int_{L_{\text{TS}}}^{L'} P^{\text{in}}(L'') dL'' \right) \right) \right) d\tau + \sqrt{D} dW_{\tau} \quad (46)$$

under Ito interpretation.

For further use, we split Eq. (46) into conceptually meaningful components. We call the total deterministic contributions to the force, the TSA force $f^{\text{TSA}}(L)$. This allows to rewrite Eq. (46) as

$$dL(\tau) = f^{\text{TSA}}(L) d\tau + \sqrt{D} dW_{\tau} . \quad (47)$$

The TSA force

$$f^{\text{TSA}}(L) = f(L) + f^{\text{A}}(L) \quad (48)$$

is comprised of two parts. A term which is exactly identical to the drift term of the forward Fokker Planck Eq. (5) and points in the same direction. Second, a “free energy force”

$$f^{\text{A}}(L) = D \frac{\partial}{\partial L} \log \left(\int_{L_{\text{TS}}}^L dL' e^{-\int^{L'} \frac{2f(L'')}{D} dL''} H(L') \right) \quad (49)$$

$$=: D \frac{\partial}{\partial L} \log Z(L) \quad (50)$$

which reverses the combined entropy production of all sample paths of the strongly terminal system. The partition function $Z(L)$ is here defined as the weighted integral over the Boltzmann factor for the sign inverted forward force $f(L)$ times the sigmoidal function

$$H(L) = 1 - \int_{L_{\text{TS}}}^L P^{\text{in}}(L') dL' . \quad (51)$$

For forward initial conditions $P^{\text{in}}(L) = \delta(L - L_f)$, the term $H(L)$ evaluates to a Heaviside step function. Above L_f only the term $f(L)$, identical to the forward dynamics, contributes. Below L_f the free energy force contributes fully.

For stochastic dynamics, the probability of the system to be found at a certain position does not only depend on the potential, but also on the possible number of states it can assume, i.e. on the entropy. When studied over all possible sample path lifetimes as implied by the construction of the TSA ensemble, the potential to be reverted is not only the integral over the force but also the entropic contribution summarized over all times, i.e. (and in analogy to stochastic thermodynamics[5]) the single particle free energy. To revert the forward force $f(L)$ and the effect of the stochastic forcing, the free energy force must be proportional to twice the force $f(L)$. Once to compensate for the forward dynamics and once to re-direct the dynamics on the free energy surface back to the forward initial conditions. The factor 2 can either be read off from the Boltzmann factor in Eq. (49), or more intuitively, by substituting the Einstein relation $D = \frac{2k_B T}{\gamma}$ [1]. k_B would be the Boltzmann constant, T the temperature and γ the friction coefficient. With this substitution it becomes apparent that the contribution due to the change in free energy comes with a factor of 2.

For an arbitrary input distribution $P^{\text{in}}(L)$, the contribution of the free energy force to the drift vanishes gradually along a sigmoidal like curve with larger values of L . This implies that above the bulk of initial positions forward and TSA dynamics are indistinguishable in their dynamical law. Below however the free energy force reverses the forward dynamics and adds additional terms which we will study below.

While the drift and diffusion terms are straight forward to transfer, the sink is not represented by the SDE Eq. (46) and needs to be handled with care. For diffusion limited reaction diffusion systems[7] it is known that a Fokker-Planck equation of the form

$$\frac{\partial}{\partial \tau} P(L, \tau) = -k(L, \tau) P(L, \tau) - \frac{\partial}{\partial L} a(L) P(L, \tau) + \frac{D}{2} \frac{\partial^2}{\partial L^2} P(L, \tau) \quad (52)$$

transforms to a Langevin equation with Ito interpretation and killing measure $k(L, \tau)$ [8, 9]. The killing measure here defines the probability $p_k = k(L, \tau) d\tau$ of a sample path to be terminated at position L at time τ . It must be evaluated in each timestep and for each sample path. Comparing terms, Eq. (52) and Eq. (45) tell us, that the killing measure for the reverse time TSA ensemble is given by

$$k(L, \tau) = \frac{P^{\text{in}}(L) \rho_{L_{\text{TS}}}(\tau|L)}{R_{L_{\text{TS}}}(L, \tau; \tau_0)} . \quad (53)$$

It defines the fraction of at time τ and position L still present sample paths that must be terminated. In general, it is surprisingly hard to correctly execute the killing measure on a single trajectory level when doing simulations. For example in the case of a delta-sink, i.e. a Robbin or radiation boundary condition, it yields the wrong result to simply terminate all sample paths that cross the sink within a finite simulation step $\Delta\tau$ with probability $p_k = k(L, \tau) \Delta\tau$. Instead, the sink crossing must be modeled as a diffusion process of duration $\Delta\tau$ and the case of not seen crossings within the simulation step $\Delta\tau$ must be included. For details we refer to Erban and Chapman[10].

For the killing measure of reverse time TSA ensembles these problems are in a sense less severe but come with a prize. Notably, the killing measure in Eq. (53) can not be executed on a trajectory by trajectory level as it depends on the full

distribution of still present sample paths $R_{L_{\text{TS}}}(L, \tau; \tau_0)$. This however suggests to simply do counting. We determine the fraction of still present sample paths N_τ , that must be killed in the space-time interval $[L, L + \Delta L] \times [\tau, \tau + \Delta \tau]$, i.e. $\frac{P^{\text{in}}(L)\rho_{L_{\text{TS}}}(\tau|L)dLd\tau}{N_\tau}$ and divide it by the fraction of sample paths $\frac{n_{\tau, \Delta L}}{N_\tau}$, which are actually in the interval. $n_{\tau, \Delta L}$ denotes the bin count. For ratios larger than one, we terminate all sample paths in the interval. For ratios smaller than one, we draw uniform random numbers and compare to the ratio. Formally this is called a metropolis criterion and we obtain the empirical killing measure

$$k(L, \tau)\Delta\tau = \min\left(1, \frac{P^{\text{in}}(L)\Delta L\rho_{L_{\text{TS}}}(\tau|L)\Delta\tau}{n_{\tau, \Delta L}\Delta L}\right). \quad (54)$$

Comparing the value of the killing measure for each trajectory at time τ to an iid random variable, this criterion allows to determine for each trajectory whether it must be terminated in the current step or not.

D. Derivation of the reverse time TSA Fokker Planck equation

Our derivation starts from the definition of the TSA ensemble for an arbitrary initial distribution $R_{l_{\text{TS}}}(L, \tau; \tau_0)$ Eq. (44), here defined in forward time t

$$R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f) = \int_{\tilde{L}_{\text{TS}}}^\infty d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}_0, t_0) R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t|\tilde{L}_0, t_0; t_f). \quad (55)$$

Using the definition of TSA sub-ensembles Eq. (28) this expression simplifies to

$$= \int_{\tilde{L}_{\text{TS}}}^\infty d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t_0). \quad (56)$$

To derive the corresponding Fokker Planck equation we take the time derivative on both sides of Eq. (55) and Eq. (56) and arrive at

$$\frac{\partial}{\partial t} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f) = \int_{\tilde{L}_{\text{TS}}}^\infty d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \frac{\partial}{\partial t} \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t_0). \quad (57)$$

Applying the Leibniz rule leads to

$$= \int_{\tilde{L}_{\text{TS}}}^\infty d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \left(\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t) + \int_{-\infty}^t dt_0 \frac{\partial}{\partial t} \left(\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t_0) \right) \right) \quad (58)$$

or equivalently

$$= \int_{\tilde{L}_{\text{TS}}}^\infty d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \left(\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) \delta(\tilde{L} - \tilde{L}_0) + \int_{-\infty}^t dt_0 \frac{\partial}{\partial t} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f|\tilde{L}_0, t_0) \right). \quad (59)$$

The first term evaluates to the hitting time distribution times the probability to be at the initial position $\tilde{L}_0$. The second term defines a double integral over the dynamics of a single contributing bridge process /sub-ensemble. We obtain

$$= \rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P^{\text{in}}(\tilde{L}) + \int_{\tilde{L}_{\text{TS}}}^\infty d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \left(\int_{-\infty}^t dt_0 \frac{\partial}{\partial t} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f|\tilde{L}_0, t_0) \right). \quad (60)$$

In the next step we substitute $\frac{\partial}{\partial t} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f|\tilde{L}_0, t_0)$ with the Fokker Planck equation of the non-normalized bridge process as derived above in this section. We substitute the dynamics in the form given by the intermediate result Eq. (19), which allows us to handle the integral over t_0 and L_0 more easily. Note, that the transition probability to reach the final state $P(\tilde{L}_f, t_f|\tilde{L}, t)$ in Eq. (19) was replaced by the hitting time probability $\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t)$, and the joint

probability $P(\tilde{L}, t, \tilde{L}_f, t_f | \tilde{L}_0, t_0)$ of the two transitions by the respective joint probability $R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f | \tilde{L}_0, t_0)$, to map the general bridge process to a bridge process which ends at a target state. The resulting evolution equation reads

$$\begin{aligned} \frac{\partial}{\partial t} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f) &= \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) P^{\text{in}}(\tilde{L}) \\ &- \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \frac{\partial}{\partial \tilde{L}} \left[f(\tilde{L}) R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f | \tilde{L}_0, t_0) - D \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) \frac{\partial}{\partial \tilde{L}} P(\tilde{L}, t | \tilde{L}_0, t_0) \right] \\ &- \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f | \tilde{L}_0, t_0). \end{aligned} \quad (61)$$

We recall that $R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f | \tilde{L}_0, t_0)$ is defined as $\rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) P(\tilde{L}, t | \tilde{L}_0, t_0)$ according to Eq. (27). This allows us to use the defining equation of $R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f)$ Eq. (56), and we arrive at the simplified evolution equation

$$\begin{aligned} &= \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) P^{\text{in}}(\tilde{L}) \\ &- \frac{\partial}{\partial \tilde{L}} \left[f(\tilde{L}) R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f) - D \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) \frac{\partial}{\partial \tilde{L}} \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 P(\tilde{L}, t | \tilde{L}_0, t_0) \right] \\ &- \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f). \end{aligned} \quad (62)$$

To obtain the guiding force and recover $R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f)$ in the second drift term as well, we multiply $\rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t)$ by $\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 P(\tilde{L}, t | \tilde{L}_0, t_0)$ both in nominator and denominator

$$\begin{aligned} &= \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) \delta(\tilde{L} - \tilde{L}_0) \\ &- \frac{\partial}{\partial \tilde{L}} \left[f(\tilde{L}) R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f) \right] \end{aligned} \quad (63)$$

$$\begin{aligned} &- \frac{D \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 P(\tilde{L}, t | \tilde{L}_0, t_0) \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t)}{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 P(\tilde{L}, t | \tilde{L}_0, t_0)} \frac{\partial}{\partial \tilde{L}} \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 P(\tilde{L}, t | \tilde{L}_0, t_0) \\ &- \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f). \end{aligned} \quad (64)$$

The nominator then evaluates to $DR_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f)$, using again Eq. (56). The denominator together with the rest of the expression can then be simplified to the form of a guiding force with L_0 and t_0 integrated out from the guiding probability. We arrive at our first intermediate result

$$\begin{aligned} &= \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) P^{\text{in}}(\tilde{L}) \\ &- \frac{\partial}{\partial \tilde{L}} \left[f(\tilde{L}) - D \frac{\partial}{\partial \tilde{L}} \log \left(\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 P(\tilde{L}, t | \tilde{L}_0, t_0) \right) \right] R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f) \\ &- \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f) \end{aligned} \quad (65)$$

in the derivation of the full reverse time TSA Fokker-Planck equation Eq. (45). Both this intermediate result and the dynamics for the free reverse time bridge Eq. (10) depend on the solution of the forward Fokker Planck $P(\tilde{L}, t | \tilde{L}_0, t_0)$. Unfortunately, explicit solutions for $P(\tilde{L}, t | \tilde{L}_0, t_0)$ are only known for very few cases. Interestingly, the above transformations have shown that it is not $P(\tilde{L}, t | \tilde{L}_0, t_0)$ but

$$Q(\tilde{L}) := \lambda \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 P(\tilde{L}, t | \tilde{L}_0, t_0) \quad (66)$$

we need an expression for. We introduce λ as a normalization factor to treat $Q(\tilde{L})$ as a normalized distribution. The normalization is necessary as $P(\tilde{L}, t | \tilde{L}_0, t_0)$ is implied with absorbing boundary conditions and decays with the hitting time distribution, as discussed above.

To derive an explicit expression for this integral we start with the forward Fokker-Planck equation

$$\frac{\partial}{\partial t} P(\tilde{L}, t | \tilde{L}_0, t_0) = -\frac{\partial}{\partial \tilde{L}} \left(f(\tilde{L}) P(\tilde{L}, t | \tilde{L}_0, t_0) \right) + \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t | \tilde{L}_0, t_0) \quad (67)$$

and integrate out the dependence on the initial time t_0

$$\int_{-\infty}^t dt_0 \frac{\partial}{\partial t} P(\tilde{L}, t | \tilde{L}_0, t_0) = \int_{-\infty}^t dt_0 \left(-\frac{\partial}{\partial \tilde{L}} \left(f(\tilde{L}) P(\tilde{L}, t | \tilde{L}_0, t_0) \right) + \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} P(\tilde{L}, t | \tilde{L}_0, t_0) \right). \quad (68)$$

To evaluate the left hand side we change to an integral over the distance $s = t - t_0$ and adapt the derivative accordingly. The resulting integral

$$\int_{-\infty}^t dt_0 \frac{\partial}{\partial t} P(\tilde{L}, t | \tilde{L}_0, t_0) = -\int_{-\infty}^0 ds \frac{\partial}{\partial s} P(\tilde{L}, s | \tilde{L}_0, 0) = -P(\tilde{L}, 0 | \tilde{L}_0, 0) = -\delta(\tilde{L} - \tilde{L}_0) \quad (69)$$

evaluates to minus the delta initial conditions of the forward process. The $+\infty$ term vanishes due to the natural boundary condition we impose. We define the non-equilibrium stationary probability density with delta insertion probability at $\tilde{L}_0$

$$Q(\tilde{L} | \tilde{L}_0) := \lambda \int_{-\infty}^t dt_0 P(\tilde{L}, t | \tilde{L}_0, t_0) = -\lambda \int_{-\infty}^0 ds P(\tilde{L}, s | \tilde{L}_0, 0) = Q(\tilde{L}, \infty | \tilde{L}_0, 0). \quad (70)$$

The generalization $Q(\tilde{L})$ Eq. (66) to arbitrary insertion probabilities is obtained by multiplication with $P^{\text{in}}(\tilde{L}_0)$ and subsequent integration over $\tilde{L}_0$. The resulting ordinary differential equation then reads

$$\begin{aligned} -\lambda P^{\text{in}}(\tilde{L}) &= -\frac{\partial}{\partial \tilde{L}} \left(f(\tilde{L}) Q(\tilde{L}) \right) + \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} Q(\tilde{L}) \\ Q(\tilde{L}_{\text{TS}}) &= 0. \end{aligned} \quad (71)$$

Integrating Eq. (71) over the full interval $\tilde{L} \in [\tilde{L}_{\text{TS}}, \infty]$ and with $\int_{\tilde{L}_{\text{TS}}}^{\infty} P^{\text{in}}(\tilde{L}') d\tilde{L}' = 1$ we find

$$\lambda = \frac{D}{2} \frac{\partial}{\partial \tilde{L}} Q(\tilde{L}_{\text{TS}}) \quad (72)$$

For completeness note, that λ , as already discussed in Zhang et. al. [11], defines a steady state probability flux at $\tilde{L}_{\text{TS}}$. Importantly equation Eq. (71) can be solved exactly. For completeness we here reproduce the result given in Zhang et. al. [11].

To solve the ordinary differential equation Eq. (71) for $Q(\tilde{L})$ we first integrate over $\tilde{L}$

$$-f(\tilde{L}') Q(\tilde{L}') \Big|_{\tilde{L}_{\text{TS}}}^{\tilde{L}} + \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} Q(\tilde{L}') \Big|_{\tilde{L}_{\text{TS}}}^{\tilde{L}} = -\lambda \int_{\tilde{L}_{\text{TS}}}^{\tilde{L}} P^{\text{in}}(\tilde{L}') d\tilde{L}' \quad (73)$$

and obtain

$$-f(\tilde{L}) Q(\tilde{L}) + \frac{D}{2} \frac{\partial}{\partial \tilde{L}} Q(\tilde{L}) = \lambda \left(1 - \int_{\tilde{L}_{\text{TS}}}^{\tilde{L}} P^{\text{in}}(\tilde{L}') d\tilde{L}' \right). \quad (74)$$

Combining the terms on the left hand side into a single expression yields

$$\frac{D}{2} e^{\int^{\tilde{L}} \frac{2f(\tilde{L}')}{D} d\tilde{L}'} \frac{\partial}{\partial \tilde{L}} \left(Q(\tilde{L}) e^{-\int^{\tilde{L}} \frac{2f(\tilde{L}')}{D} d\tilde{L}'} \right) = \lambda \left(1 - \int_{\tilde{L}_{\text{TS}}}^{\tilde{L}} P^{\text{in}}(\tilde{L}') d\tilde{L}' \right). \quad (75)$$

In the last step we again integrate from $\tilde{L}_{\text{TS}}$ to $\tilde{L}$ and solve for $Q(\tilde{L})$ to obtain

$$Q(\tilde{L}) = \frac{2\lambda}{D} e^{\int^{\tilde{L}} \frac{2f(\tilde{L}')}{D} d\tilde{L}'} \int_{\tilde{L}_{\text{TS}}}^{\tilde{L}} d\tilde{L}' e^{-\int^{\tilde{L}'} \frac{2f(\tilde{L}'')}{D} d\tilde{L}''} \left(1 - \int_{\tilde{L}_{\text{TS}}}^{\tilde{L}'} P^{\text{in}}(\tilde{L}'') d\tilde{L}'' \right), \quad (76)$$

which is the second intermediate result.

In the final step of the derivation of the full reverse time TSA dynamics we plug the obtained result for $Q(\tilde{L})$ into Eq. (65). Using the obtained result for $Q(\tilde{L})$, and $P^{\text{in}}(\tilde{L})$ as normalized distribution, we find for the guiding force

$$D \frac{\partial}{\partial \tilde{L}} \log Q(\tilde{L}) = 2f(\tilde{L}) + D \log \left(\int_{\tilde{L}_{\text{TS}}}^{\tilde{L}} d\tilde{L}' e^{-\int_{\tilde{L}'}^{\tilde{L}} \frac{2f(\tilde{L}'')}{D} d\tilde{L}''} \left(1 - \int_{\tilde{L}_{\text{TS}}}^{\tilde{L}'} P^{\text{in}}(\tilde{L}'') d\tilde{L}'' \right) \right). \quad (77)$$

With this, we obtain the final reverse time Fokker Planck written in forward time

$$\begin{aligned} \frac{\partial}{\partial t} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f) &= P^{\text{in}}(\tilde{L}) \rho_{\tilde{L}_{\text{TS}}}(t_f | \tilde{L}, t) \\ &+ \frac{\partial}{\partial \tilde{L}} \left(\left[f(\tilde{L}) + D \frac{\partial}{\partial \tilde{L}} \log \left(\int_{\tilde{L}_{\text{TS}}}^{\tilde{L}} d\tilde{L}' e^{-\int_{\tilde{L}'}^{\tilde{L}} \frac{2f(\tilde{L}'')}{D} d\tilde{L}''} \left(1 - \int_{\tilde{L}_{\text{TS}}}^{\tilde{L}'} P^{\text{in}}(\tilde{L}'') d\tilde{L}'' \right) \right) \right] R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f) \right) \\ &- \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f). \end{aligned} \quad (78)$$

To revert the time axis we set $\tau = t_f - t$, $L_f = \tilde{L}_0$ and obtain the full reverse time TSA Fokker-Planck equation as stated in Eq. (45).

III. NORMALIZED TSA DYNAMICS

The TSA ensemble $R_{L_{\text{TS}}}(L, \tau; \tau_0)$, derived in section II C, is the exact mathematical description of an ensemble of target state aligned trajectories. In reverse time more and more trajectories reach the end of their lifetime and stop to contribute to the ensemble. At $\tau \rightarrow \infty$ the ensemble vanishes. To calculate the moments of this ensemble, averages however must be taken with respect to a for each time τ normalized distribution. This normalized TSA ensemble then reads

$$R_{L_{\text{TS}}}^N(L, \tau; \tau_0) = \frac{R_{L_{\text{TS}}}(L, \tau; \tau_0)}{\int_{L_{\text{TS}}}^{\infty} dL R_{L_{\text{TS}}}(L, \tau; \tau_0)} \quad (79)$$

In this section we show that Eq. (79) can not only be obtained subsequently by normalization, but also directly from a constitutive Fokker-Planck equation. We first observe that, using the definition of $R_{L_{\text{TS}}}(L, \tau; \tau_0)$ as stated in Eq. (44) and integrating over L , the normalized TSA ensemble can be written as

$$R_{L_{\text{TS}}}^N(L, \tau; \tau_0) = \frac{R_{L_{\text{TS}}}(L, \tau; \tau_0)}{\int_{L_{\text{TS}}}^{\infty} dL_f P^{\text{in}}(L_f) \int_{\tau}^{\infty} d\tau_f \rho_{L_{\text{TS}}}(\tau_0 | L_f, \tau_f)}. \quad (80)$$

Using this definition of the normalized TSA ensemble we can derive a constitutive Fokker-Planck equation of the form

$$\begin{aligned} \frac{\partial}{\partial \tau} R_{L_{\text{TS}}}^N(L, \tau; \tau_0) &= - \frac{\rho_{L_{\text{TS}}}(\tau_0 | L, \tau) P^{\text{in}}(L) - R_{L_{\text{TS}}}^N(L, \tau; \tau_0) \int_{L_{\text{TS}}}^{\infty} dL_f P^{\text{in}}(L_f) \rho_{L_{\text{TS}}}(\tau_0 | L_f, \tau)}{\int_{L_{\text{TS}}}^{\infty} dL_f P^{\text{in}}(L_f) \int_{\tau}^{\infty} d\tau_f \rho_{L_{\text{TS}}}(\tau_0 | L_f, \tau_f)} \\ &- \frac{\partial}{\partial L} \left(\left[f(L) + D \frac{\partial}{\partial L} \log \left(\int_{L_{\text{TS}}}^L dL' e^{-\int_{L'}^L \frac{2f(L'')}{D} dL''} \left(1 - \int_{L_{\text{TS}}}^{L'} P^{\text{in}}(L'') dL'' \right) \right) \right] R_{L_{\text{TS}}}^N(L, \tau; \tau_0) \right) \\ &+ \frac{D}{2} \frac{\partial^2}{\partial L^2} R_{L_{\text{TS}}}^N(L, \tau; \tau_0). \end{aligned} \quad (81)$$

The detailed derivation is given below. Importantly, the dynamics of the with τ -decaying TSA ensemble Eq. (45) and the normalized ensemble Eq. (81) are identical. They differ however in the sink. While the un-normalized TSA dynamics loses probability mass according to their forward initial and lifetime statistics, the normalized ensemble probability mass preserving. The same amount of trajectories that are terminated are simultaneously created. Sink and source however differ in their position. While the sink is positioned according to the forward initial distribution is the source proportional to the normalized TSA ensemble at time τ and the instantaneous change in the normalization. The whole expression is then evaluated with respect to the TSA ensemble normalization.

Under these considerations, the Langevin equations of both the not- and normalized ensemble are identical. While the killing measures are identical in their location, the normalized ensemble features an additional source term that

compensates for all terminated sample paths. Reverse time trajectories in this ensemble thus not only start at $\tau = \tau_0$, but over the whole time course of the reverse time dynamics. In analogy to the discussion in section II C, the killing measure reads

$$k(L, \tau) = \frac{P^{\text{in}}(L) \rho_{L_{\text{TS}}}(\tau_0|L, \tau)}{R_{L_{\text{TS}}}(L, \tau; \tau_0)} . \quad (82)$$

Note, that the normalization of the sink and of the normalized ensemble cancel and only the un-normalized distribution $R_{L_{\text{TS}}}(L, \tau; \tau_0)$ remains. In terms of the killing measure, normalized and un-normalized TSA Langevin dynamics are thus virtually identical. For the normalized TSA ensemble additionally a source of the form

$$s(L, \tau) = \frac{\int_{L_{\text{TS}}}^{\infty} dL_f P^{\text{in}}(L_f) \rho_{L_{\text{TS}}}(\tau_0|L_f, \tau)}{\int_{L_{\text{TS}}}^{\infty} dL_f P^{\text{in}}(L_f) \int_{\tau}^{\infty} d\tau_f \rho_{L_{\text{TS}}}(\tau_0|L_f, \tau_f)} . \quad (83)$$

occurs. We note, that the source is independent of the position L and equals the instantaneous change of the normalization divided by the normalization.

The normalized TSA ensemble is clearly useful to calculate moments. From a conceptual perspective however an ensemble which creates sample paths “on the fly” is clearly not the ensemble which matches the experimental protocol of target state alignment. It thus depends on the question we ask, whether the normalized ensemble could profitable be used. With the exception of the following derivation, in the rest of this chapter we always refer to the un-normalized case and indicate if a normalized version is used.

A. Derivation of the normalized TSA dynamics

In this section we derive the normalized TSA dynamics. We start from the definition of the normalized ensemble Eq. (79) written in forward time

$$R_{\tilde{L}_{\text{TS}}}^N(\tilde{L}, t; t_f) = \frac{R_{\tilde{L}_{\text{TS}}}(\tilde{L}, t; t_f)}{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}_0, t_0)} .$$

We then substitute the definition Eq.(55) of the un-normalized ensemble

$$= \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \frac{\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t_0)}{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}_0, t_0)} , \quad (84)$$

to obtain our starting point expression. In forward time the time-derivative of the normalized ensemble reads

$$\frac{\partial}{\partial t} R_{\tilde{L}_{\text{TS}}}^N(\tilde{L}, t; t_f) = \frac{\partial}{\partial t} \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \frac{\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t_0)}{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}_0, t_0)} . \quad (85)$$

Applying the Leibniz rule we find

$$\begin{aligned} &= \frac{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t)}{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}_0, t_0)} \\ &+ \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \frac{\partial}{\partial t} \frac{\rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}, t) P(\tilde{L}, t|\tilde{L}_0, t_0)}{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(t_f|\tilde{L}_0, t_0)} . \end{aligned} \quad (86)$$

Recognizing $P(\tilde{L}, t | \tilde{L}_0, t)$ in the first term as a delta function and evaluating the time derivative in the second term then leads to

$$\begin{aligned}
&= \frac{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \rho_{\tilde{L}_{\text{TS}}}(\tilde{L}, t) \delta(\tilde{L} - \tilde{L}_0)}{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(\tilde{L}, t_0)} \\
&- \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \frac{\rho_{\tilde{L}_{\text{TS}}}(\tilde{L}, t) P(\tilde{L}, t | \tilde{L}_0, t_0) \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \rho_{\tilde{L}_{\text{TS}}}(\tilde{L}, t_0)}{\left(\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(\tilde{L}, t_0) \right)^2} \\
&+ \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \frac{\frac{\partial}{\partial t} \rho_{\tilde{L}_{\text{TS}}}(\tilde{L}, t) P(\tilde{L}, t | \tilde{L}_0, t_0)}{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(\tilde{L}, t_0)} . \tag{87}
\end{aligned}$$

We next evaluate the delta-function in the first term. The resulting term can be identified with the sink in the non-normalized reverse time TSA, here divided by the TSA-normalization. The second term can be associated as a source that ensures that the reverse time TSA stays normalized. We substitute $R_{\tilde{L}_{\text{TS}}}^N(\tilde{L}, t; t_f)$ as defined in Eq. (80) where possible. The third term describes the dynamics of the TSA ensemble as in the non-normalized ensemble Eq. (58), divided by the normalization. The normalized reverse time SDE written in forward time t then reads

$$\begin{aligned}
&= \frac{\rho_{\tilde{L}_{\text{TS}}}(\tilde{L}, t) P^{\text{in}}(\tilde{L}) - R_{\tilde{L}_{\text{TS}}}^N(\tilde{L}, t; t_f) \int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \rho_{\tilde{L}_{\text{TS}}}(\tilde{L}, t)}{\int_{\tilde{L}_{\text{TS}}}^{\infty} d\tilde{L}_0 P^{\text{in}}(\tilde{L}_0) \int_{-\infty}^t dt_0 \rho_{\tilde{L}_{\text{TS}}}(\tilde{L}, t_0)} \\
&+ \frac{\partial}{\partial \tilde{L}} \left(\left[f(\tilde{L}) + D \frac{\partial}{\partial \tilde{L}} \log \left(\int_{\tilde{L}_{\text{TS}}}^{\tilde{L}} d\tilde{L}' e^{-\int^{\tilde{L}'} \frac{2f(\tilde{L}'')}{D} d\tilde{L}''} \left(1 - \int_{\tilde{L}_{\text{TS}}}^{\tilde{L}'} P^{\text{in}}(\tilde{L}'') d\tilde{L}'' \right) \right) \right] R_{\tilde{L}_{\text{TS}}}^N(\tilde{L}, t; t_f) \right) \\
&- \frac{D}{2} \frac{\partial^2}{\partial \tilde{L}^2} R_{\tilde{L}_{\text{TS}}}^N(\tilde{L}, t; t_f) . \tag{88}
\end{aligned}$$

Switching from forward time to the reverse time description we arrive at the final expression stated in Eq. (81).

IV. EXACTLY SOLVABLE REVERSE TIME DYNAMICS

Our construction of the reverse time TSA ensemble in section II C has revealed three conceptually different approaches to obtain information on its distribution and dynamics. First, the TSA ensemble can be obtained from its definition Eq. (55). Given both the transition probability and the hitting time distribution of the forward problem are known we can construct the non-normalized bridge Eq. (27). Integration over all possible initial times and switching to the reverse time notation then leads to the reverse time TSA ensemble ending at L_f . If an initial distribution is known, it is easy to generalize the TSA ensemble to include a distribution of forward initial conditions. Below we discuss one example of this type.

The second method to obtain the reverse time TSA ensemble is based on sampling the reverse time dynamics. We derive an analytic expression for the reverse time sub-ensemble SDE Eq. (9) and synthesize sample paths with duration T drawn from the forward lifetime time distribution. Three analytically tractable cases are shown below.

The third approach is based on directly solving the full reverse time TSA Fokker Planck equation Eq. (45). We discuss one example.

A. Constructing the TSA ensemble from its definition – the random walk

TSA ensembles can be constructed from their defining equation Eq. (55), which demands to integrate over t_0 with respect to the non-normalized bridge process. We demonstrate this construction for the simple case of a target state aligned Gaussian random walk, or equivalently the diffusion process with $f(\tilde{L}) = 0$. The transition probability of a diffusion process with absorbing boundary conditions at $\tilde{L}_{\text{TS}} = 0$ is

$$P(\tilde{L}, t | \tilde{L}_0, t_0) = \frac{e^{-\frac{(\tilde{L} - \tilde{L}_0)^2}{2D(t-t_0)}} - e^{-\frac{(\tilde{L} + \tilde{L}_0)^2}{2D(t-t_0)}}}{\sqrt{2\pi D(t-t_0)}} \tag{89}$$

and can easily be obtained by using the technique of mirror charges. The lifetime (or hitting) time distribution is

$$\rho_0(t_f|\tilde{L}, t) = \frac{\tilde{L} e^{-\frac{\tilde{L}^2}{2D(t_f-t)}}}{\sqrt{2\pi D(t_f-t)^3}} \quad (90)$$

and follows directly from Eq. (26). Combining these two terms into the non-normalized bridge Eq. (27), and integrating over t_0 according to Eq. (55), we obtain

$$R_0(L, \tau; 0|L_f) = \frac{L(L + L_f - |L - L_f|)e^{-\frac{L^2}{2D\tau}}}{\sqrt{2\pi D\tau^3}}, \quad (91)$$

here written in reverse time τ and $L_f = \tilde{L}_0$. The initial time of the reverse time process is set to zero. It is the solution of the target state aligned diffusion process with delta distributed forward initial probability at $P^{\text{in}}(L) = \delta(L - L_f)$. Integrating over L we obtain the cumulative of the hitting time distribution of the random walk. The probability mass of the TSA ensemble changes proportional to the hitting time distribution Eq. (90) and thus with the rate enforced by the sink in the full reverse time TSA Fokker-Planck equation Eq. (45).

The Fokker-Planck equation for the reverse time TSA ensemble Eq. (45) can be used to directly verify this result by insertion. As the process under consideration is a random walk, for the forward force holds $f(L) = 0$. We briefly discuss this substitution for the equivalent and easier to read TSA Langevin equation Eq. (46) and therein the free energy force Eq. (49). Substituting $f(L) = 0$ into Eq. (49), the exponential simplifies to one. With delta distributed forward initial conditions, $H(L)$ becomes a step function with jump at $L = L_f$. Below L_f , the step function $H(L)$ is one and the integral inside the logarithm evaluates to L . For $L > L_f$ we find $H(L) = 0$ and thus no contribution of the free energy force to the TSA dynamics. For $L \neq L_f$, the resulting Langevin equation is

$$dL(\tau) = \begin{cases} \frac{D}{L} d\tau + \sqrt{D} dW_\tau & \text{for } L < L_f \\ \sqrt{D} dW_\tau & \text{for } L > L_f \end{cases} \quad (92)$$

The drift term of the Fokker Planck equation is thus strongly simplified and Eq. (91) can be checked by insertion. Note, that the TSA force law assumes the important form $\frac{D}{L}$ for $L < L_f$ that we will meet time and again in the following considerations. For $L = L_f$ the reverse time TSA Fokker-Planck Eq. (45) assumes a more complicated form as we must evaluate the delta initial conditions of the forward process $P^{\text{in}} = \delta(L - L_f)$ inside the free energy force, which yields a non-analytical expression. To circumvent this problem, and to demonstrate the validity of Eq. (45) for non-delta distributed forward initial conditions, we mix the TSA ensemble solutions with delta insertion Eq. (91), using a truncated Gaussian insertion probability

$$P^{\text{in}}(L_f) = \frac{\sqrt{\frac{2}{\pi}} e^{-\frac{(L_{\text{in}} - L_f)^2}{2\sigma^2}}}{\sigma \left(\text{erf}\left(\frac{L_{\text{in}}}{\sqrt{2}\sigma}\right) + 1 \right)} \quad (93)$$

normalized to the interval $L_f \in [0, \infty]$, and marginalize over L_f . We obtain the TSA reverse time ensemble

$$R_0(L, \tau; 0) = e^{-\frac{L^2 \left(\frac{g^2}{D\tau} + 1 \right) + 2L_{\text{in}}^2}{2\sigma^2}} \times \frac{L e^{\frac{L^2 + L_{\text{in}}^2}{2\sigma^2}} \left(\sqrt{2\pi} e^{\frac{L_{\text{in}}^2}{2\sigma^2}} \left((L_{\text{in}} - L) \text{erf}\left(\frac{L - L_{\text{in}}}{\sqrt{2}\sigma}\right) + L_{\text{in}} \text{erf}\left(\frac{L_{\text{in}}}{\sqrt{2}\sigma}\right) + L \right) + 2\sigma \right) - 2\sigma L e^{\frac{L_{\text{in}}(2L + L_{\text{in}})}{2\sigma^2}}}{\pi(D\tau)^{3/2} \left(\text{erf}\left(\frac{L_{\text{in}}}{\sqrt{2}\sigma}\right) + 1 \right)} \quad (94)$$

for diffusive target search starting with Gaussian insertion probability. This expression satisfies Eq. (45) with $f(L) = 0$.

B. Sampling TSA ensembles via reverse time random bridges

In this section, we discuss three different example cases for which the full TSA ensemble is explicitly constructed from fixed lifetime sub-ensembles. This can either be done by numerical integration of analytical obtainable sub-ensembles, or directly via sampling of reverse time bridge SDEs, where the lifetime is drawn from the hitting time distribution for each realization. We here discuss only the latter case for the three example cases of the Bessel, advected random walk and Ornstein-Uhlenbeck process.

1. Bessel process

The dynamical law of the Bessel process reads[12]

$$d\tilde{L}(t) = -\frac{\gamma}{\tilde{L}} dt + \sqrt{D} dW_t . \quad (95)$$

Its solution with $\gamma > 0$, absorbing boundary condition at $\tilde{L}_{\text{TS}} = 0$, and natural boundary conditions at $\tilde{L} \rightarrow \infty$ is known as Bessel process and reads[12]

$$P^{\text{fw}}(\tilde{L}, t | \tilde{L}_0, t_0 = 0) = \frac{\tilde{L}_0 e^{-\frac{\tilde{L}^2 + \tilde{L}_0^2}{2Dt}} \left(\frac{\tilde{L}}{\tilde{L}_0}\right)^{\frac{1}{2} - \frac{\gamma}{D}} I_{\frac{\gamma}{D} + \frac{1}{2}}\left(\frac{\tilde{L}\tilde{L}_0}{Dt}\right)}{Dt} . \quad (96)$$

$I_\nu(z)$ is the modified Bessel function of the first kind, with series expansion

$$I_\nu(z) = \left(\frac{z}{2}\right)^\nu \sum_{k=0}^{\infty} \frac{\left(\frac{z^2}{2}\right)^k}{k! \Gamma(\nu + k + 1)} \quad (97)$$

for real valued ν from Abramovitz & Stegun Eq. (AS 9.6.10)[13] . A derivation and the lifetime distribution

$$\rho_0(T | \tilde{L}_0) = \frac{2^{-\frac{\gamma}{D} - \frac{1}{2}} e^{-\frac{\tilde{L}_0^2}{2DT}} \left(\frac{\tilde{L}_0}{DT}\right)^{\frac{\gamma}{D} + \frac{1}{2}}}{T \Gamma\left(\frac{\gamma}{D} + \frac{1}{2}\right)} \quad (98)$$

can be found in[12, 14]. Knowing the forward probability distribution Eq. (96), the time reversed sub-ensemble SDE of this process can directly be obtained by evaluating the derivative of the logarithm of Eq. (96) using the identity

$$\frac{d}{dz} \frac{I_{\nu+\frac{1}{2}}(z)}{\sqrt{z}} = \frac{I_{\nu+\frac{3}{2}}(z)}{\sqrt{z}} + \frac{\nu I_{\nu+\frac{1}{2}}(z)}{z^{\frac{3}{2}}} \quad (99)$$

from (AS 10.2.21)[13]. We arrive at

$$dL(\tau) = \left(\frac{D}{L} - \frac{L}{(T-\tau)} + \frac{\gamma}{L} + \frac{L_f I_{\frac{\gamma}{D} + \frac{3}{2}}\left(\frac{LL_f}{D(T-\tau)}\right)}{(T-\tau) I_{\frac{\gamma}{D} + \frac{1}{2}}\left(\frac{LL_f}{D(T-\tau)}\right)} \right) d\tau + \sqrt{D} dW_\tau , \quad (100)$$

where the first term results from the power law term in Eq. (96), the second from the exponential and the last two from $I_\nu(z)$ using the stated identity. For the interpretation, recall that the initial conditions of the forward process are the final conditions of the reverse time process and thus $L_f = \tilde{L}_0$. To obtain the full result for the time reversed dynamics, we first need to solve Eq. (100) for fixed T and subsequently average over all T according to the distribution of lifetimes Eq. (98). In Fig. 4, we compare two ways to synthesize this ensemble. One generated from Eq. (95), subsequently aligned and time reverted, the other directly generated using Eq. (100) and Eq. (98). Comparing statistics of both the mean and variance, as shown in Fig. 4, confirms our calculations.

2. Advected random walk

The advected random walk changes with constant drift velocity ($\gamma > 0$) until the target state $\tilde{L}_{\text{TS}}$ is reached. Its forward SDE is

$$d\tilde{L}(t) = -\gamma dt + \sqrt{D} dW_t . \quad (101)$$

We set the absorbing boundary to $\tilde{L}_{\text{TS}} = 0$ and use natural boundary conditions at $\tilde{L} \rightarrow \infty$. The conditional probability for the forward process is

$$P^{\text{fw}}(\tilde{L}, t | \tilde{L}_0, t_0 = 0) = \frac{1}{\sqrt{2\pi Dt}} \left(e^{-\frac{(\tilde{L} + \gamma t - \tilde{L}_0)^2}{2Dt}} - e^{-\frac{(\tilde{L} + \gamma t + \tilde{L}_0)^2}{2Dt} + \frac{2\gamma \tilde{L}_0}{D}} \right) , \quad (102)$$

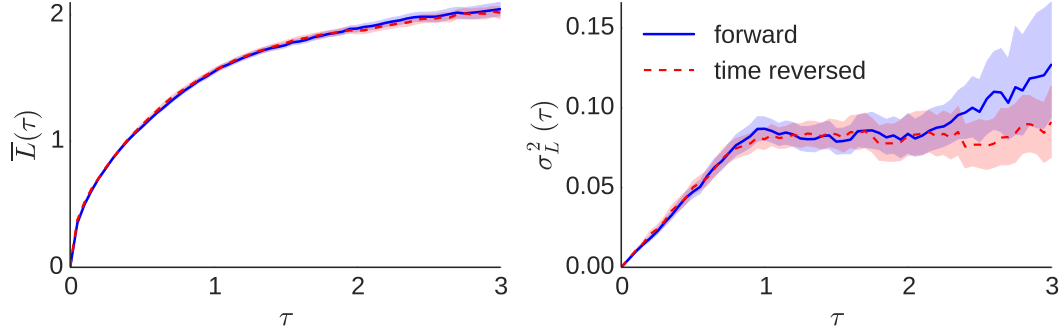


FIG. 4. **Forward (blue) and time reversed dynamics (red) show excellent agreement with respect to the Bessel process.** Shown are the mean (Left) and variance (Right) of both processes with 95% bootstrap confidence intervals. To exclude numerical inaccuracies due to rarely visited tails of Eq. (98), we directly sampled from the numerically obtained hitting time distribution of the forward process. Results were obtained using each 1000 realizations of the respective ensemble with parameter settings $\gamma = 1$, $D = 0.2$ and $\tilde{L}_0 = 2$. The larger τ , the broader the confidence intervals become, as less and less sample paths contribute to the averaging due to differences in their lengths T_i .

and the associated distribution of lifetimes is

$$\rho_0(T|\tilde{L}_0) = \frac{\tilde{L}_0}{\sqrt{2\pi DT^3}} e^{-\frac{(\tilde{L}_0 - \gamma T)^2}{2DT}}, \quad (103)$$

as given in Redner[15].

Substituting Eq. (102) into the reverse time SDE for a sub-ensemble of fixed lifetime T Eq. (9), yields

$$dL(\tau) = -\frac{L - L_f \coth(\frac{LL_f}{D(T-\tau)})}{T - \tau} d\tau + \sqrt{D} dW_\tau. \quad (104)$$

Recall that the initial conditions of the forward process are the final conditions of the reverse time process and thus $L_f = \tilde{L}_0$. Interestingly this time reversed SDE is independent of the drift velocity and thus identical to the random walk bridge. This puzzling finding is resolved when considering not only the sub-ensemble of fixed lifetime T , but the complete aligned and time reversed ensemble according to Eq. (42). Averaging all sub-ensembles defined by Eq. (104) over T with respect to the distribution of lifetimes Eq. (103), recovers the expected γ -dependence. The γ -dependence is thus fully mediated by the lifetime distribution. A numerical comparison of the forward ensemble (after time reversion and alignment), and the time reversed ensemble, defined by Eq. (104) and Eq. (103), is displayed in Fig. 5.

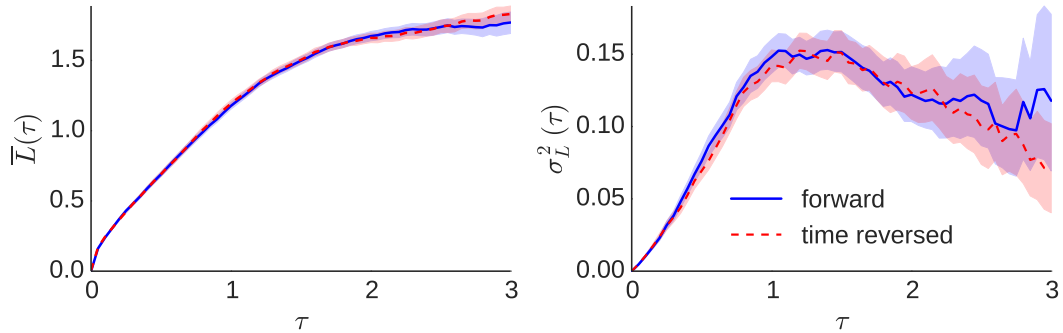


FIG. 5. **Forward (blue) and time reversed dynamics (red) of the advected random walk show excellent agreement.** Shown are the mean (Left) and variance (Right) of both processes with 95% bootstrap confidence intervals. To exclude numerical inaccuracies due to rarely visited tails of Eq. (103), we directly sampled from the numerically obtained hitting time distribution of the forward process. Results were obtained using 1000 realizations of the respective ensemble with parameter settings $\gamma = 1$, $D = 0.2$ and $\tilde{L}_0 = 2$. The larger τ , the broader the confidence intervals become, as less and less sample paths contribute to the averaging due to differences in their lengths T_i .

3. Ornstein-Uhlenbeck type process

The stochastic relaxation process describes dynamical processes with a linear restoring force. Its forward SDE is

$$d\tilde{L}(t) = -\gamma\tilde{L} dt + \sqrt{D} dW_t, \quad (105)$$

where $\gamma > 0$. The conditional probability density of this process with an absorbing boundary at $\tilde{L}_{\text{TS}} = 0$, can be constructed using the method of mirror charges. We obtain

$$P^{\text{fw}}(\tilde{L}, t | \tilde{L}_0, t_0 = 0) = \sqrt{\frac{\gamma}{\pi D(1 - e^{-2\gamma t})}} \left(e^{-\frac{\gamma(\tilde{L} - \tilde{L}_0 e^{-\gamma t})^2}{D(1 - e^{-2\gamma t})}} - e^{-\frac{\gamma(\tilde{L} + \tilde{L}_0 e^{-\gamma t})^2}{D(1 - e^{-2\gamma t})}} \right) \quad (106)$$

and the associated distribution of lifetimes T

$$\rho_0(T | \tilde{L}_0) = \frac{2D\tilde{L}_0 \left(\frac{\gamma}{D}\right)^{3/2} e^{2\gamma T - \frac{\gamma\tilde{L}_0^2}{D(e^{2\gamma T} - 1)}}}{\sqrt{\pi}(e^{2\gamma T} - 1)^{3/2}}, \quad (107)$$

given in Ricciardi and Sato[16]. Using the forward probability distribution from Eq. (106), the time reversed SDE describing sub-ensembles of length T reads

$$\begin{aligned} dL(\tau) &= \left(\gamma L + D \frac{\partial}{\partial L} \left(e^{-\frac{\gamma(L - L_f e^{-\gamma(T-\tau)})^2}{D(1 - e^{-2\gamma(T-\tau)})}} - e^{-\frac{\gamma(L + L_f e^{-\gamma(T-\tau)})^2}{D(1 - e^{-2\gamma(T-\tau)})}} \right) \right) d\tau + \sqrt{D} dW_\tau \\ &= \left(-\frac{\gamma L}{\tanh((T - \tau)\gamma)} + \frac{L_f \gamma \coth(\frac{L L_f \gamma}{D \sinh((T - \tau)\gamma)})}{\sinh((T - \tau)\gamma)} \right) d\tau + \sqrt{D} dW_\tau. \end{aligned} \quad (108)$$

Note, that the initial conditions of the forward process are now the final conditions of the reverse time process with $L_f = \tilde{L}_0$. The full aligned and time reversed ensemble is then obtained by averaging over all possible sub-ensembles, defined by Eq. (108), with respect to the distribution of lifetimes given in Eq. (107). In Fig. 6, we compare mean and variance obtained by terminal alignment of Eq. (105), and directly from Eq. (108) sampling lifetimes from Eq. (107). We find excellent agreement.

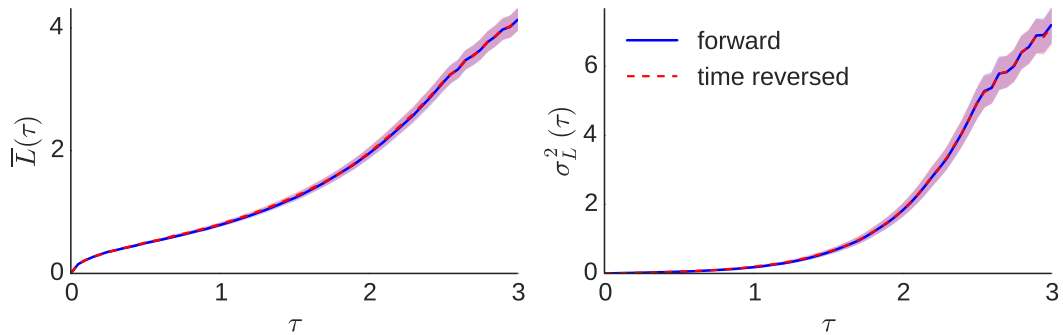


FIG. 6. Forward (blue) and time reversed dynamics (red) of Ornstein-Uhlenbeck type processes agree excellent. Shown are the mean (Left) and variance (Right) of both processes with 95% bootstrap confidence intervals. To exclude numerical inaccuracies due to rarely visited tails of Eq. (107), we directly sampled from the numerically obtained hitting time distribution of the forward process. Results were obtained using 1000 realizations of sample paths with parameter settings $\gamma = 1$, $D = 0.2$ and $\tilde{L}_0 = 10$. Unlike for the previous examples, we used a larger value for $\tilde{L}_0$ to reveal the interesting concave convex shape of the mean, which, for too small $\tilde{L}_0$ values, is not detectable. The larger τ , the broader the confidence intervals become, as less and less sample paths contribute to the averaging due to differences in their lifetimes T_i .

C. Constructing TSA ensembles from their reverse time TSA Fokker-Planck equation – the Bessel process

The third approach to obtain the density of complete reverse time TSA ensembles, directly solves the defining Fokker-Planck Eq. (45) or SDE Eq. (46). We here consider the case of the Bessel process for which this approach is analytically tractable. The forward process is defined by Eq. (95) with initial condition $L_f = \tilde{L}_0$. The probability density which describes the forward process is given by Eq. (96). Defined as a TSA ensemble the SDE for the Bessel process reads

$$dL(\tau) = \left(-\frac{\gamma}{L} + D \frac{\partial}{\partial L} \log \left(\int_0^L dL' L'^{\frac{2\gamma}{D}} \Theta(\tilde{L}_0 - L') \right) \right) d\tau + \sqrt{D} dW_\tau, \quad (109)$$

where we substituted $f(L) = -\frac{\gamma}{L}$ into Eq. (46). We assume $L_{TS} = 0$ and $L_f = \tilde{L}_0$. For $L \neq L_f$ this SDE simplifies to

$$dL(\tau) = \begin{cases} \frac{\gamma+D}{L} d\tau + \sqrt{D} dW_\tau & \text{for } L < L_f \\ -\frac{\gamma}{L} d\tau + \sqrt{D} dW_\tau & \text{for } L > L_f, \end{cases} \quad (110)$$

which both have known solutions in terms of their transition probability densities when defined on the complete interval $L \in [0, \infty]$ [12]. These solutions can be used to piece wise solve the full SDE. We start with the solution of the process defined in Eq. (110) for $L < L_f$, but assume for the moment, that we are interested in the solution on the complete interval $L \in [0, \infty]$. The transition probability, for arbitrary L_0 , which describes this process, is then given as [12]

$$P^<(L, \tau | L_0, \tau_0 = 0) = \frac{L e^{-\frac{L^2 + L_0^2}{2D\tau}} \left(\frac{L}{L_0} \right)^{\frac{\gamma}{D} + \frac{1}{2}} I_{\frac{\gamma}{D} + \frac{1}{2}} \left(\frac{LL_0}{D\tau} \right)}{D\tau}. \quad (111)$$

Using the series expansion of $I_\nu(z)$ Eq. (97) from Abramovitz & Stegun (AS 9.9.10) [13], we can evaluate this process for $L_0 \rightarrow 0$ and obtain

$$P^<(L, \tau | L_0 = 0, \tau_0 = 0) = \frac{2^{-\frac{\gamma}{D} - \frac{1}{2}} (D\tau)^{-\frac{\gamma}{D} - \frac{3}{2}} e^{-\frac{L^2}{2D\tau}} L^{\frac{2\gamma}{D} + 2}}{\Gamma\left(\frac{\gamma}{D} + \frac{3}{2}\right)}. \quad (112)$$

The needed contribution of the sub-process defined in Eq. (110) ($L > L_f$) is more complicated to obtain, as its transition probability Eq. (96) goes to zero for $L_0 \rightarrow L_{TS}$. We first guess, that the L dependent part of the solution of Eq. (110) ($L > L_f$), now defined on $L \in [0, \infty]$, can be obtained by first normalizing the known solution of the Bessel process Eq. (96). The resulting ensemble consists of sample paths which at time t have not been absorbed at the target state but are generated by the process defined in Eq. (110) ($L > L_f$). We then take the limit $L_0 \rightarrow L_{TS}$. The normalization is simply done by the cumulative of the hitting time distribution stated in Eq. (98). The seeked expression for $L_0 \rightarrow 0$ then reads

$$P^>(L, \tau | L_0 = 0, \tau_0 = 0) \propto \lim_{L_0 \rightarrow 0} \frac{L_0 e^{-\frac{L^2 + L_0^2}{2D\tau}} \left(\frac{L}{L_0} \right)^{\frac{1}{2} - \frac{\gamma}{D}} I_{\frac{\gamma}{D} + \frac{1}{2}} \left(\frac{LL_0}{D\tau} \right)}{D\tau \left(1 - \frac{\Gamma\left(\frac{\gamma}{D} + \frac{1}{2}, \frac{L_0^2}{2D\tau}\right)}{\Gamma\left(\frac{\gamma}{D} + \frac{1}{2}\right)} \right)} = \frac{L e^{-\frac{L^2}{2D\tau}}}{D\tau}, \quad (113)$$

where $(>)$ denotes the forward force law $-\frac{\gamma}{L}$. To find the limit $L_0 \rightarrow 0$ we again use the zero-th order of the series expansion for $I_\nu(z)$ stated in Eq. (97). With the help of Eq.(AS 6.5.3), Eq.(AS 6.5.4) and Eq.(AS 6.5.29) [13], we replace the upper incomplete gamma function in the denominator of Eq. (113) by the series

$$\Gamma(\nu, z) = \Gamma(\nu) - z^\nu \sum_{n=0}^{\infty} \frac{(-z)^n}{(\nu + n)n!} \quad \text{for } |z| < \infty. \quad (114)$$

The zero-th order cancels the one in the denominator. The next order cancels all remaining L_0 -terms of the nominator. The resulting term is proportional to the probability density of those sample paths which have survived until τ and started at $L_{TS} = 0$.

In the next step, we combine Eq. (111) and Eq. (113) into one expression which solves Eq. (109). Assuming continuity but not differentiability at $L = L_f$, we can easily connect the two solutions at L_f , as Eq. (113) is fully included in Eq. (111). We obtain

$$R_0(L, \tau; 0|L_f) = \begin{cases} \frac{2(2D\tau)^{-\frac{\gamma}{D}-\frac{3}{2}} e^{-\frac{L_f^2}{2D\tau}} L^{\frac{2\gamma}{D}+2}}{\Gamma(\frac{\gamma}{D}+\frac{3}{2})} & L < L_f \\ \frac{2(2D\tau)^{-\frac{\gamma}{D}-\frac{3}{2}} e^{-\frac{L_f^2}{2D\tau}} L_f^{\frac{2\gamma}{D}+1}}{\Gamma(\frac{\gamma}{D}+\frac{3}{2})} & L \geq L_f \end{cases} \quad (115)$$

For $L \neq L_f$, we confirm this solution by insertion into the Fokker-Planck equation corresponding to Eq. (110). Furthermore, integrating $R_0(L, \tau; 0|L_f)$ over L yields one minus the cumulative of the forward hitting time Eq. (98) and shows that $R_0(L, \tau; 0|L_f)$ from Eq. (115) decays with the rate given by the hitting time distribution as demanded by the reverse time TSA Fokker Planck equation Eq. (45). As L_{TS} , according to the Feller boundary classification[14] is an entrance boundary and the other boundary is a natural boundary all lost probability mass must be due to the kink of $R_0(L, \tau; 0|L_f)$ at L_f , i.e. due to the sink at $\delta(L - L_f)$. This confirms that Eq. (115) is the full solution of the reverse time TSA Fokker-Planck associated with Eq. (109).

To calculate mean and variance with respect to all not yet killed sample paths of the reverse-time ensemble, we normalize Eq. (115) to unity with respect to L for all times τ . We obtain for the mean

$$\bar{L}(\tau) = \frac{A1 + A2}{B} \quad (116)$$

with

$$\begin{aligned} A1 &= e^{\frac{L_f^2}{2D\tau}} \left(\sqrt{2\pi D\tau} L_f^{\frac{2\gamma}{D}+1} \operatorname{erfc} \left(\frac{L_f}{\sqrt{2D\tau}} \right) + 2(2D\tau)^{\frac{\gamma}{D}+1} \left(\Gamma \left(\frac{\gamma}{D} + 2 \right) - \Gamma \left(\frac{\gamma}{D} + 2, \frac{L_f^2}{2D\tau} \right) \right) \right) \\ A2 &= 2L_f^{\frac{2(\gamma+D)}{D}} \\ B &= 2L_f^{\frac{2\gamma}{D}+1} + 2(2D\tau)^{\frac{\gamma}{D}+\frac{1}{2}} e^{\frac{L_f^2}{2D\tau}} \left(\Gamma \left(\frac{\gamma}{D} + \frac{3}{2} \right) - \Gamma \left(\frac{\gamma}{D} + \frac{3}{2}, \frac{L_f^2}{2D\tau} \right) \right) \end{aligned}$$

and for the variance

$$\sigma_L^2(\tau) = \frac{(2D\tau)^{\frac{\gamma}{D}+\frac{3}{2}} e^{\frac{L_f^2}{2D\tau}} \left(\Gamma \left(\frac{\gamma}{D} + \frac{5}{2} \right) - \Gamma \left(\frac{\gamma}{D} + \frac{5}{2}, \frac{L_f^2}{2D\tau} \right) \right) + L_f^{\frac{2\gamma}{D}+1} (2D\tau + L_f^2)}{L_f^{\frac{2\gamma}{D}+1} + (2D\tau)^{\frac{\gamma}{D}+\frac{1}{2}} e^{\frac{L_f^2}{2D\tau}} \left(\Gamma \left(\frac{\gamma}{D} + \frac{3}{2} \right) - \Gamma \left(\frac{\gamma}{D} + \frac{3}{2}, \frac{L_f^2}{2D\tau} \right) \right)} - \bar{L}(\tau)^2. \quad (117)$$

Both mean and variance are depicted in Fig. 4b of the main text.

V. TSA DYNAMICS CLOSE TO THE TARGET STATE

The dynamics valid for final stages of convergence to the target state can be characterized by a single SDE valid for all forward initial conditions. This claim is easily verified by inspecting Eq. (46). For L sufficiently below the bulk of the forward initial distribution $P^{\text{in}}(L)$, the term $H(L) = 1 - \int_{L_{TS}}^L P^{\text{in}}(L') dL'$, which describes the influence of the forward initial conditions on the reverse time TSA dynamics, evaluates to approximately one. If most of the sample paths have not yet reached the sink at $P^{\text{in}}(L)$, this further implies that almost no sample path has terminated in reverse time. The killing measure $k(L, \tau)$ (Eq. (53)), i.e. the product of hitting time and initial distribution normalized to the current number of still existing sample paths, therefore defines a sector of the $L-\tau$ plane, where, for $k(L, \tau) \approx 0$, TSA ensembles are – up to exponentially small corrections – governed by

$$dL(\tau) = \left(f(L) + D \frac{\partial}{\partial L} \log \left(\int_{L_{TS}}^L dL' e^{-\int_{L'}^L \frac{2f(L'')}{D} dL''} \right) \right) d\tau + \sqrt{D} dW_\tau. \quad (118)$$

This form of the reverse time TSA ensemble, valid for final stages of convergence to the target state, provides a powerful tool to infer forward dynamics irrespective of unknown initial conditions.

The reverse time SDE for TSA ensembles close to completion Eq. (118) can be analytically expressed for a broad class of forward forces. Exemplary, we study the properties of power law like forward dynamics with force term

$$f(\tilde{L}) = -\gamma \tilde{L}^\alpha, \quad (119)$$

with $\gamma > 0$, $\alpha \in \mathbb{R}$ and constant additive noise D . We derive analytical expressions for the free energy force using forward forces of the form Eq. (119). We check their validity numerically and use the derived expressions to characterize general time-reversed ensembles near the target state.

The TSA reverse time dynamics for forward dynamics Eq. (119) are

$$dL(\tau) = \left(-\gamma L^\alpha + \frac{(D\alpha + D) \left(-\frac{2\gamma}{D\alpha + D} \right)^{\frac{1}{\alpha+1}} e^{\frac{2\gamma L^{\alpha+1}}{D\alpha + D}}}{\Theta(\alpha + 1) \Gamma\left(\frac{1}{\alpha+1}\right) - \Gamma\left(\frac{1}{\alpha+1}, -\frac{2\gamma L^{\alpha+1}}{D\alpha + D}\right)} \right) d\tau + \sqrt{D} dW_\tau \quad \alpha \neq -1, \quad (120)$$

where $\Gamma(z)$ is the gamma-function, $\Gamma(\nu, z)$ the upper incomplete gamma function and $\Theta(\nu)$ the Heaviside step function. The case for $\alpha = -1$ connecting $\alpha > 1$ and $\alpha < 1$ is the Bessel process with reverse time TSA dynamics

$$dL(\tau) = \frac{\gamma + D}{L} d\tau + \sqrt{D} dW_\tau \quad \alpha = -1. \quad (121)$$

A detailed derivation and an exemplary comparison to the exact dynamics, already discussed in section IV B 1, is provided below.

A. TSA dynamics independent from forward initial conditions

In this section we derive reverse time TSA dynamics under the assumption that the forward initial conditions are spatially and temporally well separated from the target state. We derive Eq. (120) for a forward force of the form $f(\tilde{L}) = -\gamma \tilde{L}^\alpha$, as stated in Eq. (119).

We start from the definition of the reverse time alignment force as stated in Eq. (49) for general reverse time TSA dynamics with

$$f^A(L) = D \frac{\partial}{\partial L} \log \tilde{I}(L), \quad (122)$$

where the integral

$$\tilde{I}(L) = \int_0^L e^{\frac{2\Phi(L')}{D}} H(L') dL' \quad (123)$$

takes the form of a canonical partition function for the potential

$$\Phi(L) = - \int^L f(L') dL', \quad (124)$$

associated with the sign inverted forward force. The influence of the forward initial conditions on the TSA dynamics is captured by $H(L)$ Eq. (51). It is a sigmoidal like function, which is one at the target state and decreases the closer L is to the bulk of the forward initial condition. It approaches zero beyond. For well separated target states and forward initial conditions we can therefore safely set $H(L) = 1$, close to L_{TS} , and define $I(L) = \tilde{I}(L)|_{H(L)=1}$.

The derivation of Eq. (120) then starts with evaluating the potential

$$\Phi(L) = \int^L \gamma L'^\alpha dL' = \frac{\gamma L^{\alpha+1}}{\alpha+1} \quad \alpha \neq -1. \quad (125)$$

Substituting the resulting $\Phi(L)$ into $I(L)$ and with help of Eq. (AS 6.5.25) from Abramowitz & Stegun[13], yields

$$I(L) = \tilde{C}(\alpha) \Gamma\left(\frac{1}{\alpha+1}, -\frac{2\gamma L^{\alpha+1}}{D(\alpha+1)}\right) \Big|_0^L \quad \alpha \neq -1, \quad (126)$$

where $\Gamma(n, z)$ is the upper incomplete gamma function and $\tilde{C}(\alpha) := -\frac{1}{\alpha+1} \left(-\frac{2\gamma}{D(\alpha+1)}\right)^{-\frac{1}{\alpha+1}}$ is a prefactor depending on α and independent of L . Depending on α , the lower boundary assumes two different values. For $\alpha > -1$, the argument $z := -\frac{2\gamma L^{\alpha+1}}{D(\alpha+1)}$ of the upper incomplete gamma function $\Gamma(\nu, z)$, goes to zero and $\Gamma(\nu, z)$ reduces to $\Gamma(\nu)$. For $\alpha < -1$, the argument z diverges ($z \rightarrow \infty$) as $L \rightarrow 0$ and $\Gamma(\nu, z) \rightarrow 0$, as can be read off from Eq. (AS 6.5.32) in Abramowitz & Stegun[13]. Combined into a single expression using the Heaviside step-function $\Theta(\nu)$ we arrive at

$$I(L) = \tilde{C}(\alpha) \left(\Gamma\left(\frac{1}{\alpha+1}, -\frac{2\gamma L^{\alpha+1}}{D(\alpha+1)}\right) - \Theta(\alpha+1) \Gamma\left(\frac{1}{\alpha+1}\right) \right) \quad \alpha \neq -1. \quad (127)$$

To obtain the final expression for the free energy force $f^{\mathcal{A}}$ we rewrite

$$f^{\mathcal{A}}(L) = D \frac{\partial}{\partial L} \log I(L) = \frac{D}{I(L)} \frac{\partial}{\partial L} I(L), \quad (128)$$

which allows us to directly read off the sought expression, as $\frac{\partial}{\partial L} I(L)$ is simply the integrand of $I(L)$, and obtain

$$f^{\mathcal{A}}(L) = \frac{(D\alpha + D) \left(-\frac{2\gamma}{D\alpha + D}\right)^{\frac{1}{\alpha+1}} e^{\frac{2\gamma L^{\alpha+1}}{D\alpha + D}}}{\Theta(\alpha+1) \Gamma\left(\frac{1}{\alpha+1}\right) - \Gamma\left(\frac{1}{\alpha+1}, -\frac{2\gamma L^{\alpha+1}}{D\alpha + D}\right)} \quad \alpha \neq -1. \quad (129)$$

Substituting the resulting $f^{\mathcal{A}}(L)$ into the equation for the time reversed SDE Eq. (118) yields the final result as stated in Eq. (120).

B. Comparing TSA dynamics with and without forward initial conditions

To demonstrate the excellent agreement of the TSA approximation stated in Eq. (120) and Eq. (121) with the corresponding aligned forward simulations close to completion we use the three, from section IV known, analytically tractable example cases of constriction ($\alpha = -1$), advection ($\alpha = 0$) and relaxation ($\alpha = 1$). From above, we further know, that the TSA-approximation of well separated initial and final conditions breaks down, when a relevant fraction of time reversed sample paths reaches the level of the initial state of the forward process. To observe this phenomenon, we state the initial conditions of the forward process explicitly and adapt the plot range accordingly.

1. Bessel process

The Bessel process within the TSA close to completion approximation is given by Eq. (121). Fig. 7 shows the

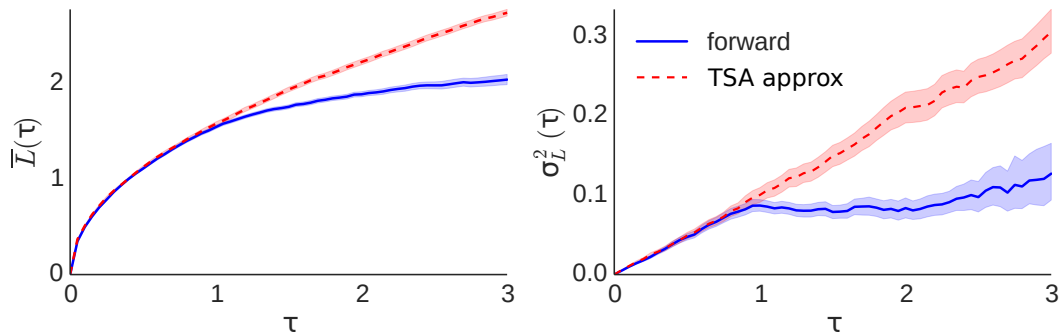


FIG. 7. **Forward dynamics (blue) and the approximate time reversed TSA dynamics (red) of the Bessel process agree excellent close to the target state.** Shown are the mean (Left) and variance (Right) of both processes with 95% bootstrap confidence intervals. Results were obtained using 1000 realizations for each of the respective ensemble with parameter settings $\gamma = 1$, $D = 0.2$ and $\tilde{L}_{\text{in}} = 2$.

comparison between this approximation and the corresponding exact forward process starting at $\tilde{L}_{\text{in}} = 2$. Close to completion clearly both mean and variance are very well reproduced by Eq. (121).

Important for benchmark tests in section VIC, Eq. (121) can be solved analytically and results in the transition probability stated in Eq. (111).

Specifying Eq. (111) with respect to the initial conditions $(L_0, \tau_0) = (0, 0)$ yields Eq. (112), which can be used to obtain expressions for mean

$$\bar{L}(\tau) = \frac{\sqrt{2}\sqrt{D}\tau\Gamma(\frac{\gamma}{D} + 2)}{\Gamma(\frac{\gamma}{D} + \frac{3}{2})} \quad (130)$$

and variance

$$\sigma_L^2(\tau) = D\tau \left(\frac{2\gamma}{D} - \frac{2\Gamma(\frac{\gamma}{D} + 2)^2}{\Gamma(\frac{\gamma}{D} + \frac{3}{2})^2} + 3 \right). \quad (131)$$

Forming the joint probability distribution $P(L, \tau, L', \tau')$ from Eq. (111) and Eq. (112) we obtain the two-time covariance function

$$C_L(\tau, \tau') = \frac{2D\Gamma(\frac{\gamma}{D} + 2)^2 \left(\sqrt{\tau'\tau}^{-\frac{\gamma}{D}-2} (\tau - \tau')^{\frac{\gamma}{D}+\frac{5}{2}} {}_2F_1\left(\frac{\gamma}{D} + 2, \frac{\gamma}{D} + 2; \frac{\gamma}{D} + \frac{3}{2}; \frac{\tau'}{\tau}\right) - \sqrt{\tau'\tau} \right)}{\Gamma(\frac{\gamma}{D} + \frac{3}{2})^2} \quad (132)$$

stated for $\tau > \tau'$, where ${}_2F_1(a, b; c; z)$ is the Gaussian hypergeometric function. The obtained mean Eq. (130), variance Eq. (131) and two-time covariance Eq. (132) are later in this text used as a baseline reference for further derivations.

2. Advected random walk

Assuming advection and thus $\alpha = 0$, the TSA approximation close to completion stated in Eq. (120) simplifies to

$$dL = \gamma \left(\frac{2}{1 - e^{-\frac{2\gamma L}{D}}} - 1 \right) d\tau + \sqrt{D} dW_\tau. \quad (133)$$

Close to completion, the dynamics match both in mean and variance with the exact aligned forward simulation as displayed in Fig. 8. With help of Eq. (133), we can now explain the general behavior of aligned advection processes

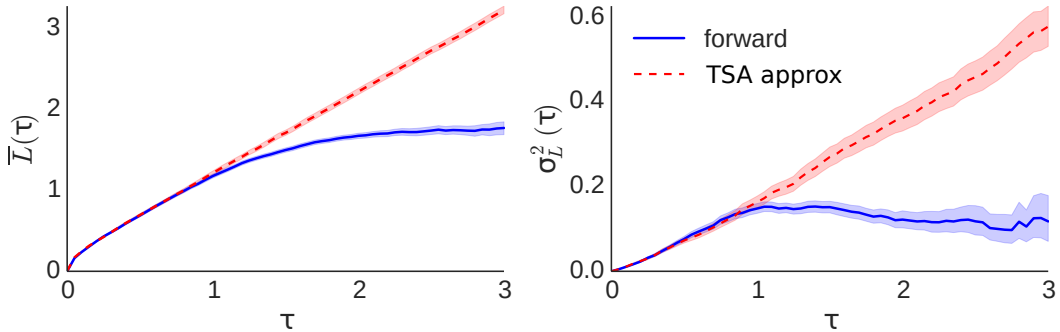


FIG. 8. **Forward dynamics (blue) and the approximate time reversed TSA dynamics (red) of the advected random walk agree excellent close to the target state.** Shown are the mean (Left) and variance (Right) of both processes with 95% bootstrap confidence intervals. Results were obtained using each 1000 realizations of the respective ensemble with parameter settings $\gamma = 1$, $D = 0.2$ and $\tilde{L}_{\text{in}} = 2$.

close to completion. For small L , Eq. (133) reduces to $\frac{D}{L}$ and induces a square root like behavior of the mean (see main text or Eq. (130) ($\gamma = 0$)). Further away from the absorbing boundary, the time reversed force term simplifies to γ , yielding a linear behavior of the mean. Then, eventually, the influence of the initial conditions ($\tilde{L}_{\text{in}} = 2$) of the forward process can not any longer be neglected and the approximated and exact mean start to deviate.

3. Ornstein-Uhlenbeck type process

The TSA-approximation of well separated initial and final conditions Eq. (120) reduces for the case of relaxation ($\alpha = 1$) to the form

$$dL = \left(-\gamma L + \frac{\sqrt{\gamma D}}{F(L\sqrt{\frac{\gamma}{D}})} \right) d\tau + \sqrt{D} dW_\tau, \quad (134)$$

where $F(x) = e^{-x^2} \int_0^x e^{y^2} dy$ is the Dawson integral[13]. In Fig. 9, we compare this approximation with the forward

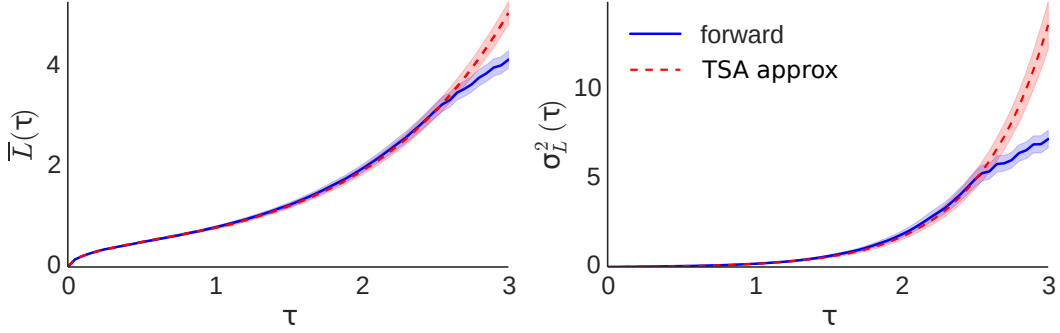


FIG. 9. **Forward dynamics (blue) and the approximate time reversed TSA dynamics (red) of an Ornstein-Uhlenbeck type process agree excellent close to the target state.** Shown are the mean (Left) and variance (Right) of both processes with 95% bootstrap confidence intervals. Results were obtained using each 1000 realizations of the respective ensemble with parameter settings $\gamma = 1$, $D = 0.2$ and $\tilde{L}_{\text{in}} = 10$.

simulation. In particularly noteworthy here is the behavior of the mean, changing from a root like to a convex shape. We further observe that the approximate variance is a convex function, which seems to be a preserved feature of all processes with $\alpha > 0$.

VI. SMALL L AND WEAK NOISE APPROXIMATION – STRONGLY AND WEAKLY TERMINAL TSA DYNAMICS

Depending on the form of the force law $f(\tilde{L})$, dynamics close to the target state are either dominated by the deterministic drift or by random fluctuations which eventually determine when a trajectory reaches the target state. We coined the dynamics *weakly terminal* if the target state approach is dominated by random fluctuation and otherwise *strongly terminal*. To quantitatively characterize this effect we assume, that sufficiently close to the target state, most dynamics are well approximated by a power law. Evaluating a small L -expansion of Eq. (120) then yields separable contributions due to the forward force law and due to the noise. Evaluating the limit $L \rightarrow L_{\text{TS}}$ allows to characterize which contribution dominates.

We start our derivation with the expansion of Eq. (120) for small L . The behavior of the expansion depends on the argument of both the upper incomplete gamma function and the exponential $\left| \frac{2\gamma L^{\alpha+1}}{D(\alpha+1)} \right|$ and whether it diverges or vanishes for $L \rightarrow 0$. If we only consider L then its behavior is clear and we observe divergence for $\alpha < -1$ and convergence for $\alpha > -1$. If we, however, additionally demand that our results should not deteriorate in the limit of small noise, i.e. $L \rightarrow 0$ and $D \rightarrow 0$, then the case $-1 < \alpha < 0$ switches its class and starts to diverge for $L \rightarrow 0$. A detailed argument and derivation is given below in this section. We here only state the results for the two regimes $\alpha \geq 0$ and $\alpha < 0$.

For $\alpha \geq 0$ the reverse time SDE Eq. (120) reduces to

$$dL(\tau) = \left(\frac{D}{L} - \gamma \frac{\alpha}{\alpha+2} L^\alpha + \mathcal{O}\left(\frac{L^{2\alpha+1}}{D}\right) \right) d\tau + \sqrt{D} dW_\tau \quad \alpha \geq 0. \quad (135)$$

Independent of the exact value of α , the force that drives the time reverse ensemble away from $\tilde{L}_{\text{TS}}$ is thus always the pure free energy force $\frac{D}{L}$ as exhibited by the random walk case Eq. (92). This finding has important implications

for the reconstruction of $f(L)$ from TSA data. Close to $\tilde{L}_{\text{TS}}$ all time reversed processes with $\alpha \geq 0$ mimic pure diffusion. The identification of genuine forces has thus to rely on dynamics sufficiently far away from $\tilde{L}_{\text{TS}}$. For larger values of L , however, higher order terms can no longer be neglected. Their contributions mix and no clear universal approximation is achievable. We conclude, that a reliable reconstruction of the genuine force $f(L)$ for $\alpha > 0$ is only possible using the full time reversed expression as stated in Eq. (120).

For $\alpha < 0$, and for $-1 < \alpha < 0$ only under the assumption of small noise ($D \rightarrow 0$), Eq. (120) reduces to

$$dL(\tau) = \left(\gamma L^\alpha - \frac{\alpha D}{L} + \mathcal{O}\left(\frac{D^2}{L^{2+\alpha}}\right) \right) d\tau + \sqrt{D} dW_\tau \quad \alpha < 0. \quad (136)$$

For $\alpha < -1$, and for $0 < \alpha < -1$ given sufficiently small noise, the TSA dynamics close to the target state are fully governed by the sign inverted forward force law plus a contribution due to the noise similar to Eq. (135), however, here reweight by a factor α . We note that the case $\alpha = -1$, i.e. the reverse time Bessel process Eq. (121), is exactly included in Eq. (136). Dynamics with $\alpha < 0$ should thus be distinguishable by inspecting their behavior near the target state.

In summary, Eq. (135) and Eq. (136) together allow to distinguish between weakly terminal Eq. (135) and strongly terminal Eq. (136) TSA dynamics close to the target state. The weakly terminal case ($\alpha \geq 0$) close to the target state is indistinguishable from a pure TSA random walk with free energy force $\frac{D}{L}$. This process is a Bessel process and fully characterized by the transition probability density Eq. (111) ($\gamma = 0$) and Eq. (112) ($\gamma = 0$). To form expectations about TSA ensemble data, we calculate then mean, variance and two-time correlation function below in this section.

The strongly terminal case ($\alpha < 0$) has a non negligible contribution due to the sign inverted forward force close to the target state. This sensitivity to the parameter of the forward dynamics close to L_{TS} motivates to seek for a small noise expansion around the sign inverted forward law. Further below, we demonstrate, that expressions for mean, variance and two-time correlation function can be obtained in the limit of small noise.

A. The derivation of the small L expansion

The expansion of $f^A(L)$ Eq. (129) depends on the limit properties of the argument $z = -\frac{2L^{\alpha+1}\gamma}{\alpha D + D}$ of the rewritten free energy force

$$f^A(L) = \frac{C(D)e^{-z}}{\Theta(\frac{1}{\nu})\Gamma(\nu) - \Gamma(\nu, z)} \quad \alpha \neq -1 \quad (137)$$

and whether the limit of $|z|$, with respect to D and L , rather approaches zero or infinity. For readability, we collect all non z -dependent terms into

$$C(D) = (D\alpha + D) \left(-\frac{2\gamma}{D\alpha + D} \right)^{\frac{1}{\alpha+1}} \quad (138)$$

and set $\nu = \frac{1}{1+\alpha}$. In the following three subsections we discuss the expansion of $f^A(z)$ with respect to z , given small L , for the regimes $\alpha \in (-\infty, -1), (-1, \infty)$. We then reassess the reverse time forces in the interval $\alpha \in (-1, 0)$ and with respect to its dependency on the size of the diffusion constant D .

1. The case $|z| \rightarrow 0$

For $\alpha > -1$ ($\nu > 0$) the expansion variable $|z|$ decreases with decreasing L . For these cases the denominator of Eq. (137) can be written as

$$\Gamma(\nu) - \Gamma(\nu, z) = \Gamma(\nu) z^\nu e^{-z} \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(\nu + n + 1)} \quad \text{for } |z| < \infty, \quad (139)$$

using Eq. (AS 6.5.3), Eq. (AS 6.5.4) and Eq. (AS 6.5.29)[13]. The free energy force $f^A(L)$ is

$$f^A(L) = \frac{C(D)}{\Gamma(\nu) z^\nu \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(\nu + n + 1)}} \quad \alpha > -1, \quad (140)$$

where we canceled the exponential function in nominator and denominator. Truncating the series in the denominator to include only the terms up to first order, we arrive at

$$f^{\mathcal{A}}(L) = \frac{\nu C(D) z^{-\nu}}{1 + \frac{z}{\nu+1} + \mathcal{O}(z^2)} \quad \alpha > -1 . \quad (141)$$

We here used the recurrent relation $\Gamma(\nu+1) = \nu\Gamma(\nu)$ from Eq. (AS 6.1.15) Abramowitz & Stegun[13] to simplify the expression. In the last step we approximate the denominator to lowest order in z and obtain

$$f^{\mathcal{A}}(L) = \nu C(D) z^{-\nu} \left(1 - \frac{z}{\nu+1} + \mathcal{O}(z^2) \right) \quad \alpha > -1 . \quad (142)$$

Replacing the effective parameters and variable z with the original parameters ν, γ, D and variable L , we arrive at the small L expansion

$$f^{\mathcal{A}}(L) = \frac{D}{L} + \frac{2\gamma L^\alpha}{\alpha+2} + \mathcal{O}\left(\frac{L^{1+2\alpha}}{D}\right) \quad \alpha > -1 . \quad (143)$$

Substituting Eq. (143) into Eq. (118) we arrive at the small L -expansion stated in Eq. (135).

2. The case $|z| \rightarrow \infty$

For $\alpha < -1$ ($\nu < 0$) the expansion variable z goes to infinity for small L . With $\nu < 0$ the Heaviside step function evaluates to zero and the denominator simplifies to $\Gamma(\nu, z)$ which we expand for large z , using the known asymptotic expansion Eq. (AS 6.5.32)[13]

$$\Gamma(\nu, z) = z^{\nu-1} e^{-z} \left(1 + \frac{\nu-1}{z} + \mathcal{O}(z^{-2}) \right) \quad \text{for } |z| \rightarrow \infty . \quad (144)$$

We substitute this expansion into Eq. (137) and arrive at

$$f^{\mathcal{A}}(L) = -\frac{C(D) z^{1-\nu}}{1 + \frac{\nu-1}{z} + \mathcal{O}(z^{-2})} \quad \alpha < -1 \quad (145)$$

after canceling the exponential terms. In a final step we approximate the denominator for $z \rightarrow \infty$, i.e. Taylor expand for small orders of $1/z$, and obtain

$$f^{\mathcal{A}}(L) = -C(D) z^{1-\nu} \left(1 - \frac{\nu-1}{z} + \mathcal{O}(z^{-2}) \right) \quad \alpha < -1 . \quad (146)$$

Re-substituting the original parameters and variable L , the final free energy force reads

$$f^{\mathcal{A}}(L) = 2\gamma L^\alpha - \frac{\alpha D}{L} + \mathcal{O}\left(\frac{D^2}{L^{2+\alpha}}\right) \quad \alpha < -1 . \quad (147)$$

3. The L and D dependent range $-1 < \alpha < 0$

For α in the range $-1 < \alpha < 0$, the value of the expansion variable z depends on the choice of the diffusion constant D . For large D the limit behavior of z is fully defined by L and we find

$$\lim_{L \rightarrow 0} |z| = \lim_{L \rightarrow 0} \left| -\frac{2L^{\alpha+1}\gamma}{\alpha D + D} \right| = 0 \quad \text{for } -1 < \alpha < 0 . \quad (148)$$

If we additionally assume, that the expansion holds in the limit of small noise, the limiting behavior changes and we find

$$\lim_{L \rightarrow 0, D \rightarrow 0} |z| = \lim_{L \rightarrow 0, D \rightarrow 0} \left| -\frac{2L^{\alpha+1}\gamma}{\alpha D + D} \right| = \infty \quad \text{for } -1 < \alpha < 0 . \quad (149)$$

This implies, that for a given L , we can always find a small enough D so that the expansion variable z becomes large. Thus, we also consider $|z| \rightarrow \infty$ in the regime $-1 < \alpha < 0$. Under this condition, the $\Theta(\alpha + 1)$ dependent term in the denominator of Eq. (137) does no longer vanish automatically. Eq. (145) then reads

$$f^{\mathcal{A}}(L) = -\frac{C(D)z^{1-\nu}}{m(z) + 1 + \frac{\nu-1}{z} + \mathcal{O}(z^{-2})} \quad \alpha < -1 \quad (150)$$

with

$$m(z) = -e^z z^{1-\nu} \Gamma(\nu) . \quad (151)$$

In the following we argue, that $m(z)$ becomes negligible for large $|z|$. We show, that the limes of $m(z)$ with respect to $D \rightarrow 0$ is zero and conclude, that we can always find a D , which is small enough to neglect $m(z)$ in the expansion of $f^{\mathcal{A}}(L)$. For small D , Eq. (150) therefore follows the same expansion as the case $\alpha < -1$ discussed before.

To proof these statements, we first recall, that $z = -\frac{2L^{1+\alpha}\gamma}{(1+\alpha)D}$ is negative for $-1 < \alpha < 0$. The exponential thus decays with increasing $|z|$. With $\nu = \frac{1}{1+\alpha}$, the exponent $1 - \nu$ is negative for $-1 < \alpha < 0$ and the power law $|z|^{1-\nu}$ decays with increasing $|z|$. For $|z| \rightarrow \infty$ we therefore find

$$\lim_{|z| \rightarrow \infty} |m(z)| = 0 \quad \text{for} \quad -1 < \alpha < 0 . \quad (152)$$

We next show, that $|m(z)|$ also approaches zero for $D \rightarrow 0$. We start by rewriting $m(z)$ in terms of α, γ, D and L and obtain

$$m(L) = \Gamma\left(\frac{1}{\alpha+1}\right) L^\alpha \left(-\frac{2\gamma}{D(1+\alpha)}\right)^{\frac{\alpha}{\alpha+1}} e^{-\frac{2\gamma L^{\alpha+1}}{D(1+\alpha)}} . \quad (153)$$

To clarify the behavior of the first D -dependent term we note, that its absolute value can be written as $\left|-\frac{2\gamma}{D(1+\alpha)}\right|^{\frac{\alpha}{\alpha+1}} = \left|\frac{D(1-|\alpha|)}{2\gamma}\right|^{\frac{1-|\alpha|}{|\alpha|}}$. With $|\alpha| \in (0, 1)$, the exponent is greater than zero and the full term goes to zero for $D \rightarrow 0$. The second D dependent term in Eq. (153) is the exponential. For $D \rightarrow 0$ the exponent goes to $-\infty$ and the exponential vanishes. We can therefore write

$$\lim_{D \rightarrow 0} |m(L)| = 0 \quad \text{for} \quad -1 < \alpha < 0 . \quad (154)$$

In the final step we show that $|m(L)|$ also vanishes in the simultaneous limit of $D \rightarrow 0$ and $L \rightarrow 0$. To perform this limit we set w.l.o.g. $D = L$ and rewrite Eq. (153) accordingly. In the resulting equation

$$m(L) = \Gamma\left(\frac{1}{\alpha+1}\right) L^{\frac{\alpha^2}{1+\alpha}} \left(-\frac{2\gamma}{1+\alpha}\right)^{\frac{\alpha}{\alpha+1}} e^{-\frac{2\gamma L^\alpha}{1+\alpha}} , \quad (155)$$

we can directly read off that the power law $L^{\frac{\alpha^2}{1+\alpha}}$ decays to zero for decreasing L , as does the exponential. We conclude, that

$$\lim_{\substack{L \rightarrow 0, D \rightarrow 0 \\ D \sim L}} |m(L)| = 0 \quad \text{for} \quad -1 < \alpha < 0 \quad (156)$$

holds. It is thus always possible to find a small enough D , where the large z expansion of $f^{\mathcal{A}}(L)$, discussed above, holds also in the regime $-1 < \alpha < 0$.

We conclude this section by a remark. Reinspecting Eq. (153) we observe, that all D 's are multiplied by $1 + \alpha$. For α decreasing from zero to minus one we therefore expect $m(L)$ to become smaller and smaller until it approaches zero for $\alpha \rightarrow -1$ using the very same argument as for D . The large $|z|$ expansion will therefore hold for the larger D values, the closer α is to -1 .

B. Moments and universal correlation function for weakly terminal TSA ensembles

For $\alpha > 0$, the SDE Eq. (135) with respect to the free energy force $f^A(L)$ expanded in small L tells us, that the dynamics close to the target state are purely governed by the force term $\frac{D}{L}$. From section IV A, or simply by inserting $f(L) = 0$ into Eq. (118), we know, that the SDE

$$dL(\tau) = \frac{D}{L}d\tau + \sqrt{D} dW_\tau \quad (157)$$

describes the dynamics of a TSA random walk close to the target state and well separated from its forward initial conditions. For completeness and easy use we here state the mean

$$\bar{L}(\tau) = \sqrt{\frac{8D\tau}{\pi}}, \quad (158)$$

variance

$$\sigma_L^2(\tau) = \frac{(3\pi - 8)D\tau}{\pi} \quad (159)$$

and two-time covariance

$$C_L(\tau, \tau') = \begin{cases} \frac{2D(-4\sqrt{\tau\tau'} + 3\sqrt{\tau(\tau' - \tau)} + (2\tau + \tau') \sin^{-1}(\sqrt{\frac{\tau}{\tau'}}))}{\pi} & \text{for } \tau < \tau' \\ \sigma_L^2(\tau) & \text{for } \tau = \tau' \\ \frac{2D(-4\sqrt{\tau'\tau} + 3\sqrt{\tau'(\tau - \tau')} + (2\tau' + \tau) \sin^{-1}(\sqrt{\frac{\tau'}{\tau}}))}{\pi} & \text{for } \tau > \tau' . \end{cases} \quad (160)$$

They can be obtained either from the known transition probability Eq. (111) and density Eq. (112) of the Bessel process with an entrance boundary at $L_{\text{TS}} = 0$ and in the limit $\gamma \rightarrow 0$, or from the moments stated in section IV B 1. Using the obtained variance and covariance, the correlation function $c_L(\tau, \tau') = C_L(\tau, \tau')/(\sigma_L(\tau)\sigma_L(\tau'))$ reads

$$c_L(\tau, \tau') = \begin{cases} \frac{2(-4\sqrt{\tau\tau'} + 3\sqrt{\tau(\tau' - \tau)} + (2\tau + \tau') \sin^{-1}(\sqrt{\frac{\tau}{\tau'}}))}{(3\pi - 8)\sqrt{\tau\tau'}} & \text{for } \tau < \tau' \\ 1 & \text{for } \tau = \tau' \\ \frac{2(-4\sqrt{\tau'\tau} + 3\sqrt{\tau'(\tau - \tau')} + (2\tau' + \tau) \sin^{-1}(\sqrt{\frac{\tau'}{\tau}}))}{(3\pi - 8)\sqrt{\tau'\tau}} & \text{for } \tau > \tau' . \end{cases} \quad (161)$$

Let us briefly discuss the obtained reverse time moments. For the mean, we observe that it grows with $\sqrt{\tau}$. It is thus similar to a forward random walk which starts at the boundary but never returns to it. Such a random walk can be constructed from Eq. (89) (random walk with mirror charges), after normalization to one (for every τ), and in the limit $\tilde{L} \rightarrow 0$. The result is the same we obtained as an intermediate step in the derivation of the exact TSA reverse time Bessel process Eq. (113)

$$P(L, \tau) = \frac{Le^{-\frac{L^2}{2D\tau}}}{D\tau} \quad (162)$$

and is known as a Rayleigh distribution. For the mean of this restricted random walk we find

$$\bar{L}(\tau) = \sqrt{\frac{\pi D\tau}{2}}, \quad (163)$$

which shows the same τ dependence as the mean of the TSA random walk Eq. (158) but with a different pre-factor. This observations motivates to also study the variance of the restricted random walk

$$\sigma_L^2(\tau) = \frac{1}{2}(4 - \pi)D\tau . \quad (164)$$

We again find the same dependence on τ as in the variance of the TSA random walk but again a different pre-factor. This shows, that fitting mean or variance independently can lead to wrong conclusions. Comparing for example the

squared coefficient of variation $C_V^2 = \frac{\sigma_L^2(\tau)}{\bar{L}^2(\tau)}$ we find the two different constants $C_{V \text{ TSA-rw}}^2 = \frac{3\pi}{8} - 1 \approx 0.18$ for the TSA random walk and $C_{V \text{ rest-rw}}^2 = \frac{4}{\pi} - 1 \approx 0.27$ for the restricted random walk. This shows the TSA random walk, as one might have assumed, is not the same as a restricted random walk.

While sample paths in both cases are generated by the same dynamics, they differ in the selection of sample paths which contribute to the ensemble. In the TSA ensemble, sample paths in principle have had the time to explore the full half plane $L \in [0, \infty]$ before they reach the target state. The fraction of sample paths which predominantly “walk” in one direction close to the target state is therefore enriched compared to a restricted random walk, which only neglects all sample paths which ever return to the initial conditions. Formally, it's the difference between a TSA ensemble and a meander process[2], which never returns to its initial position. For mathematical details on meander processes we refer to Majumdar and Orland[2].

C. Moments for strongly terminal TSA ensembles

For $\alpha < -1$ and for $-1 < \alpha < 0$ under the additional constraint of small D , TSA dynamics are strongly terminal close to the target state. This motivates to try a small noise expansion around the deterministic time reversed dynamics to obtain expression for the moments of the SDE Eq. (136). We adopt the approach defined for a standard SDE (see Gardiner chapter 6.2[1]) to include order D drift terms and find for the mean

$$\bar{L}(\tau) = ((1 - \alpha)\gamma\tau)^{\frac{1}{1-\alpha}} + D \frac{(7\alpha - 3)((1 - \alpha)\gamma\tau)^{\frac{\alpha}{\alpha-1}}}{4(3\alpha - 1)\gamma} + \mathcal{O}(D^{3/2}), \quad (165)$$

variance

$$\sigma_L^2(\tau) = D \frac{1 - \alpha}{1 - 3\alpha} \tau + \mathcal{O}(D^2) \quad (166)$$

and covariance

$$C_L(\tau, \tau') = \begin{cases} \left(\frac{\tau}{\tau'}\right)^{\frac{\alpha}{\alpha-1}} \sigma_L^2(\tau) + \mathcal{O}(D^2) & \text{for } \tau < \tau' \\ \left(\frac{\tau'}{\tau}\right)^{\frac{\alpha}{\alpha-1}} \sigma_L^2(\tau') + \mathcal{O}(D^2) & \text{for } \tau > \tau' \\ \sigma_L^2(\tau) + \mathcal{O}(D^2) & \text{for } \tau = \tau' \end{cases} \quad (167)$$

by a perturbation theory calculation around the deterministic solution of Eq. (136) in the Diffusion constant up to order D . The correlation function $c_L(\tau, \tau') = C_L(\tau, \tau')/(\sigma_L(\tau)\sigma_L(\tau'))$ reads

$$c_L(\tau, \tau') = \begin{cases} \left(\frac{\tau}{\tau'}\right)^{\frac{3}{2} + \frac{1}{\alpha-1}} & \text{for } \tau < \tau' \\ \left(\frac{\tau'}{\tau}\right)^{\frac{3}{2} + \frac{1}{\alpha-1}} & \text{for } \tau > \tau' \\ 1 & \text{for } \tau = \tau' \end{cases} \quad (168)$$

Note, that for all expressions (Eq. (165)-Eq. (168)) boundary conditions are already implicitly included due to the contribution of the free energy force. We further recall, that the expansion stated in Eq. (136) was truncated at order D . Only terms up to this order are therefore considered in Eq. (165), Eq. (166) and Eq. (167). Given this approximation, we have shown above in this section, that only the mean Eq. (165) carries a relevant contribution from the approximate free energy force $-\frac{\alpha D}{L}$.

The obtained expression can be used to infer power law forward forces $f(L) = -\gamma L^\alpha$ from TSA ensembles in the limit of small noise. For example, starting from the two-time correlation function, we read off the power law exponent α . With α we can fit the variance and determine the diffusion constant D . The force strength γ is obtained from the mean.

For the small noise approximation to hold well, and as a rule of thumb, the squared coefficient of variation $C_V^2 = \frac{\sigma_L^2(\tau)}{\bar{L}^2(\tau)}$, approximated as the lowest order small noise terms, should be well below one. For example for $\alpha = -1$ this implies $C_V^2 = D/(4\gamma) < 1$. For all other α -values we find $C_V^2 \sim \tau^{\frac{\alpha+1}{\alpha-1}}$. The approximation thus becomes better the larger τ given $-1 < \alpha < 0$, and for $\alpha < -1$ the smaller τ . In the following, we will briefly comment on the expressions for $\bar{L}(\tau)$, $\sigma_L^2(\tau)$ and $C_L(\tau, \tau')$, and present a more detailed discussion and a step by step derivation below.

The mean $\bar{L}(\tau)$ (Eq. (165)) is given as the deterministic solution to Eq. (136) ($D \rightarrow 0$) plus a (for all $\alpha < 0$) solely positive contribution of order D . The case $\alpha < 0$ thus shows, that a purely deterministic approach to extract the mean from any experimentally obtained and terminally aligned data is bound to fail. As the mean, given by Eq. (165), adds up a deterministic term and a deterministic positive contribution due to the noise, a pure deterministic approach overestimates the underlying forward force by the contribution of the noise. The difference between the deterministic approximation (order D^0 of Eq. (165)) and the correct analytic obtainable solution Eq. (130) is exemplary shown in Fig. 10 (Left) for the case $\alpha = -1$. To be precise, in Fig. 10 we compare the exact solution of the TSA Bessel

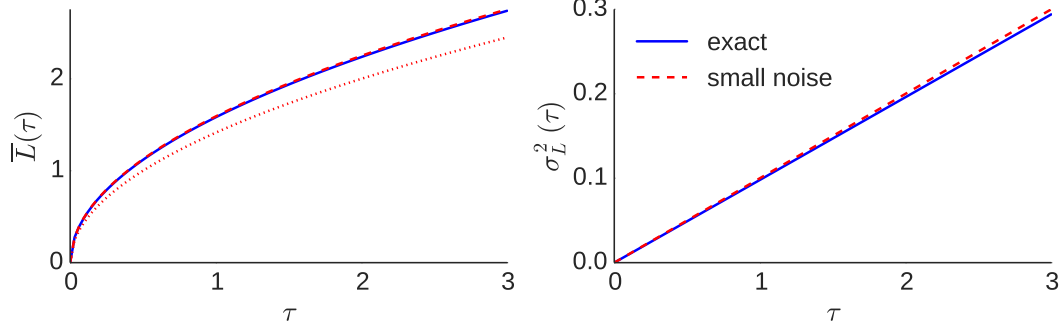


FIG. 10. **The small noise approximation up to order D is an excellent approximation of the exact dynamics.** Shown are small noise expressions (red) for the mean (Left) Eq. (165) and variance (Right) Eq. (166) in comparison to the exact analytic expressions (blue), as stated in Eq. (130) Eq. (131) for the Bessel process. For the small noise expression of the mean we additionally show the curve up to order D^0 (dotted). Curves are obtained for the parameters $\alpha = -1$, $\gamma = 1$, $D = 0.2$.

process with forward initial conditions shifted to infinity, and the small noise approximation stated in Eq. (165) and Eq. (166). We find excellent agreement.

The variance $\sigma_L^2(\tau)$, up to order D (Eq. (166)) is a γ -independent function linearly growing with $D\tau$. It thus shows the same dependence on $D\tau$ as the exact variance result Eq. (131) for the Bessel process SDE Eq. (136) with $\alpha = -1$. Furthermore, if we assume $D/\gamma \rightarrow 0$, the variance for $\alpha = -1$, as stated in Eq. (131) approaches the small noise solution from below until both assume the form $\frac{D\tau}{2}$. Taken together this indicates that in the limit of small noise, characterized by the C_V^2 , all relevant features of $\sigma_L^2(\tau)$ and $C_L(\tau, \tau')$, are capture within an expansion up to order D . To further test this for general $\alpha < 0$ we compare numerical solutions of Eq. (136) with our analytic small noise expressions for mean Eq. (165) and variance Eq. (166). Results for $\alpha = -0.5$ and $\alpha = -2$ are displayed in Fig. 11 and compared to the case $\alpha = -1$. All considered, we conclude that $\bar{L}(\tau)$ and $\sigma_L^2(\tau)$, as stated in Eq. (165) and Eq. (166),

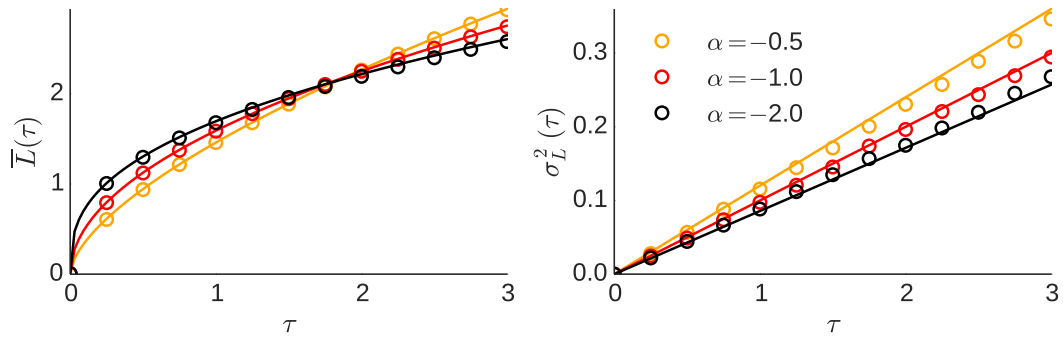


FIG. 11. **The small noise expansion is a very good approximation of its underlying TSA-SDE.** Comparison between a numerical evaluation of Eq. (136) (circles) and its approximation as analytic small noise expansion up to order D^1 (lines) as given in Eq. (165) and Eq. (166). Shown are mean (Left) and variance (Right) for the cases $\alpha = -1/2$ (orange), $\alpha = -1$ (red) and $\alpha = -2$ (black). All other parameters are chosen identical with $\gamma = 1$ and $D = 0.2$.

are sufficient to reconstruct $f(L)$ and D for general $\alpha < 0$ and in the limit of small noise.

The two-time covariance function $C_L(\tau, \tau')$ is highly informative for force reconstruction. If enough sample paths are available ($\mathcal{O}(100) - \mathcal{O}(1000)$), the covariance stated in Eq. (167) is suitable to uniquely infer both the general form of the forward force $f(L)$ and the noise level.

The fraction $C_L(\tau, \tau')/(\sigma_L(\tau)\sigma_L(\tau'))$ represents the two time correlation function $c_L(\tau, \tau')$. With its sole dependence on α , $c_L(\tau, \tau')$ uniquely fixes the general form of the force law, irrespective of the reconstructed γ and the noise level D . To check for the quality of Eq. (168), we compare in Fig. 12 the case $\alpha = -1$ to its analytical counterpart obtained from Eq. (131) and Eq. (132). Using the same parameters as already in Fig. 10 we observe in Fig. 12 (Right) a

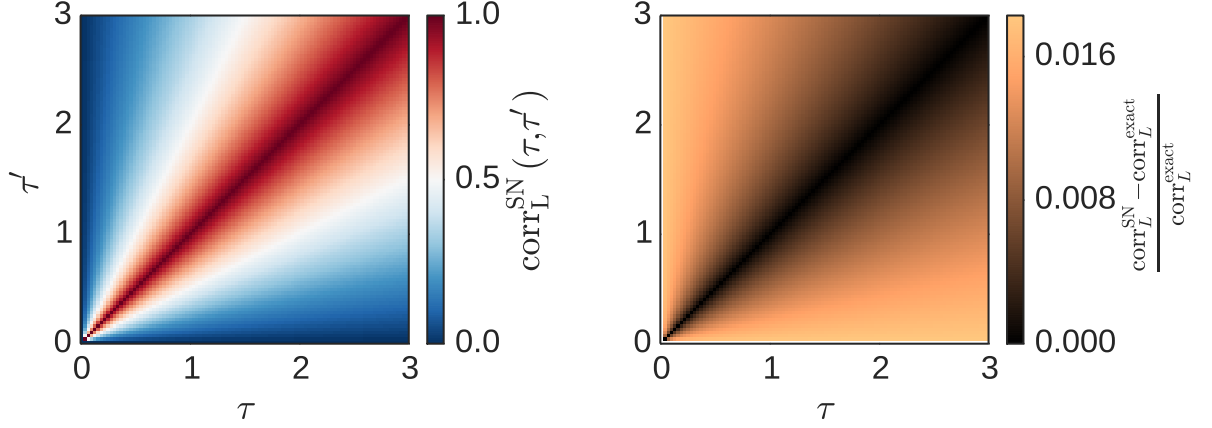


FIG. 12. **The small noise approximation of the correlation function is an excellent approximation of the exact dynamics.** Shown is the small noise correlation function as given by Eq. (168) for the case $\alpha = -1$ (Left) and its deviations from the known exact correlation function of the Bessel process (Right) directly obtainable from Eq. (131) and Eq. (132).

maximal deviation of 2% for large correlation times, and even smaller deviations for shorter correlation times.

Interestingly, the 2d representation of $c_L(\tau, \tau')$ as stated in Eq. (168) and displayed for the cases $\alpha = -0.5$ and $\alpha = -2$ in Fig. 13, shows an easy to identify signature. Due to the sole dependence of Eq. (168) on the ratio of τ

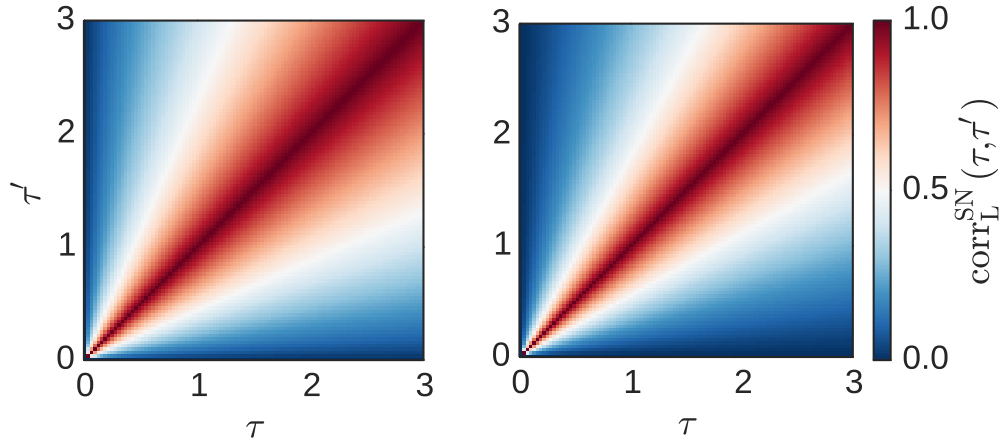


FIG. 13. **Exemplary correlation functions obtained from the analytic small noise expression as stated in Eq. (168).** Shown are the cases $\alpha = -1/2$ (Left) and $\alpha = -2$ (Right). The two remaining parameters are chosen identical with $\gamma = 1$ and $D = 0.2$. For both we observe characteristic straight equi-value lines as demanded by Eq. (168).

and τ' the 2d correlation function exhibits straight level lines ($\tau' = \text{const} \cdot \tau$). Given we are in the regime of small noise and do not observe this straight line structure in our experimental data, we can thus directly exclude all pure forward force laws of the form stated in Eq. (119) with $\alpha < 0$. We further know from above, that processes with $\alpha \geq 0$ follow a force law D/L close to completion. The respective correlation function can be calculated and is stated in Eq. (161). Connecting the two cases $\alpha < 0$ and $\alpha > 0$ we now have a theoretical understanding of the mean, variance and two-time correlation close to target states.

1. *Weak noise approximation of moments for strongly terminal TSA ensembles*

Starting from Eq. (136), we here derive the expressions Eq. (165)-Eq. (168) for mean $\bar{L}(\tau)$, variance $\sigma_L^2(\tau)$, covariance $C_L(\tau, \tau')$ and the correlation function $c_L(\tau, \tau')$. The calculation is valid in the domain $\alpha < 0$, as discussed above, and in the limit of small noise. With some minor modifications we follow the weak noise approximation approach discussed in Gardiner (chapter 6.2)[1].

The derivation starts with rewriting Eq. (136) in the general form

$$dL = a(L)d\tau + \epsilon^2 b(L)d\tau + \epsilon dW_\tau \quad (169)$$

with $\sqrt{D}$ substituted by the expansion parameter ϵ . For small ϵ we expand

$$L(\tau) = L_0(\tau) + \epsilon L_1(\tau) + \epsilon^2 L_2(\tau) + \dots \quad (170)$$

around the deterministic solution $L_0(\tau)$. We further assume that we can write

$$a(L) = a(L_0 + \epsilon L_1 + \epsilon^2 L_2 + \dots) = a_0(L_0) + \epsilon a_1(L_0, L_1) + \epsilon^2 a_2(L_0, L_1, L_2) + \dots \quad (171)$$

The general expression for $a(L)$ then reads

$$a(L) = a \left(L_0 + \sum_{m=1}^{\infty} \epsilon^m L_m \right) = \sum_{p=0}^{\infty} \frac{1}{p!} \frac{d^p a(L_0)}{dL_0} \left(\sum_{m=0}^{\infty} \epsilon^m L_m \right)^p \quad (172)$$

and after sorting terms we find for the first three terms

$$a_0(L_0) = a(L_0) \quad (173)$$

$$a_1(L_0, L_1) = L_1 \frac{da(L_0)}{dL_0} \quad (174)$$

$$a_2(L_0, L_1, L_2) = L_2 \frac{da(L_0)}{dL_0} + \frac{1}{2} L_1^2 \frac{d^2 a(L_0)}{dL_0^2} \quad (175)$$

The same procedure can be applied to $b(L)$. Taken together the equations to lowest order in ϵ are

$$dL_0 = a(L_0)d\tau \quad (176)$$

$$dL_1 = a_1(L_1, L_0)d\tau + dW_\tau \quad (177)$$

$$dL_2 = a_2(L_2, L_1, L_0)d\tau + b(L_0)d\tau \quad (178)$$

The first of these equations is the deterministic equation

$$dL_0 = \gamma L_0^\alpha d\tau \quad (179)$$

As the process starts at the boundary at $L_0(0) = 0$, its solution is simply given as

$$L_0 = ((1 - \alpha)\gamma\tau)^{\frac{1}{1-\alpha}} \quad \text{with } \alpha < 0 \quad (180)$$

The second equation Eq. (177) describes a generalized Ornstein-Uhlenbeck process

$$dL_1 = k(L_0(\tau)) L_1 d\tau + dW_\tau \quad (181)$$

with the time-dependent drift coefficient

$$k(L_0) = \frac{da(L_0)}{dL_0} = \gamma \frac{dL_0^\alpha}{dL_0} = \gamma \alpha L_0^{\alpha-1} \quad (182)$$

Inserting the solution for $L_0(\tau)$ we find

$$k(L_0) = \gamma \alpha ((1 - \alpha)\gamma\tau)^{-1} \quad (183)$$

Employing the initial conditions $L_1(0) = 0$, the solution of equation Eq. (181) reads

$$L_1(\tau) = \int_0^\tau e^{\int_{\tau'}^\tau k(L_0(s))ds} dW_{\tau'} = \int_0^\tau \left(\frac{\tau}{\tau'} \right)^{-\frac{\alpha}{\alpha-1}} dW_{\tau'} \quad (184)$$

Together, Eq. (180) for $L_0(\tau)$ and Eq. (184) for $L_1(\tau)$ form the basis of all further calculations. Inserting these solutions into the expansion stated in Eq. (170) and taking the ensemble average we obtain expressions for mean

$$\langle L(\tau) \rangle = \langle L_0(\tau) \rangle + \epsilon \langle L_1(\tau) \rangle + \dots, \quad (185)$$

variance

$$\sigma_L^2(\tau) = \langle (L(\tau) - \langle L(\tau) \rangle)^2 \rangle = \epsilon^2 \langle L_1^2(\tau) \rangle + \dots \quad (186)$$

and two the time covariance

$$C(\tau, \tau') = \langle (L(\tau) - \langle L(\tau) \rangle) (L(\tau') - \langle L(\tau') \rangle) \rangle = \epsilon^2 \langle L_1(\tau) L_1(\tau') \rangle + \dots \quad (187)$$

in lowest order of ϵ and valid for $\alpha < 0$. We first evaluate these expressions to lowest order, which for $\sigma_L^2(\tau)$ and $C_L(\tau, \tau')$ is already at order $\mathcal{O}(D)$. Corrections for the mean up to order $\mathcal{O}(D)$ are evaluated subsequently. Note, that the average over a single Wiener integral, such as $\langle L_1(\tau) \rangle$ always evaluates to zero and therefore corrections to the mean will be of order ϵ^2 .

To 0th order, the solution for the mean is equivalent to the deterministic solution Eq. (180). For the variance, we have to calculate the second moment of equation Eq. (184), i.e.

$$\begin{aligned} \sigma_L^2(\tau) &= D \langle L_1^2(\tau) \rangle = D \int_0^\tau \int_0^\tau \left(\frac{\tau}{\tau'} \right)^{-\frac{\alpha}{\alpha-1}} \left(\frac{\tau}{\tau''} \right)^{-\frac{\alpha}{\alpha-1}} dW_{\tau'} dW_{\tau''} \\ &= D \int_0^\tau \left(\frac{\tau}{\tau'} \right)^{-\frac{2\alpha}{\alpha-1}} d\tau' = D \frac{1-\alpha}{1-3\alpha} \tau \quad \text{for } \alpha < 0, \end{aligned} \quad (188)$$

where we replace ϵ^2 by the original D . Note that $\langle L_1 \rangle^2 = 0$ and thus drops out of the calculation. Similarly, we obtain the two-time covariance function

$$\begin{aligned} C(\tau, \tau') &= D \int_0^\tau \int_0^{\tau'} \left(\frac{\tau}{s} \right)^{-\frac{\alpha}{\alpha-1}} \left(\frac{\tau'}{s'} \right)^{-\frac{\alpha}{\alpha-1}} dW_s dW_{s'} \\ &= D \int_0^{\min(\tau, \tau')} \left(\frac{\tau}{s} \right)^{-\frac{\alpha}{\alpha-1}} \left(\frac{\tau'}{s} \right)^{-\frac{\alpha}{\alpha-1}} ds \\ &= \begin{cases} D \frac{(\alpha-1)\tau^{\frac{1}{\alpha-1}+2}\tau'^{-\frac{\alpha}{\alpha-1}}}{3\alpha-1} & \text{for } \tau < \tau' \\ D \frac{(\alpha-1)\tau'^{\frac{1}{\alpha-1}+2}\tau^{-\frac{\alpha}{\alpha-1}}}{3\alpha-1} & \text{for } \tau > \tau' \\ D \langle L_1^2(\tau) \rangle & \text{for } \tau = \tau' \end{cases} \quad \text{and } \alpha < 0 \end{aligned} \quad (189)$$

again in terms of D . Using the variance Eq. (188), we can rewrite this result in the final form stated in Eq. (166). The two-time correlation function also directly follows from Eq. (189). Using the definition

$$c(\tau, \tau') := \frac{C(\tau, \tau')}{\sigma_L(\tau)\sigma_L(\tau')} \quad (190)$$

we obtain the final form stated in Eq. (168).

In a last step we calculate the first D -dependent contribution to the mean, characterizing deviations from the deterministic solution. As contributions due to $L_1(\tau)$ average out, terms of order ϵ^2 become important and thus the contribution $-\alpha D/L$ of the free energy force as stated in Eq. (136). Using the series expansion of $L(\tau)$ in orders of ϵ as stated in Eq. (170), we next evaluate the contribution of $L_2(\tau)$ to the mean. This is most simply achieved by directly evaluating an averaged Eq. (178). Using the specifications due to Eq. (175) we then obtain a linear differential equation

$$\frac{d\langle L_2 \rangle}{d\tau} = \frac{da(L_0)}{dL_0} \langle L_2 \rangle + \frac{1}{2} \frac{d^2 a(L_0)}{dL_0^2} \langle L_1^2 \rangle - \frac{\alpha}{L_0} \quad (191)$$

with the solution

$$\langle L_2(\tau) \rangle = \frac{(7\alpha-3)((1-\alpha)\gamma\tau)^{\frac{\alpha}{\alpha-1}}}{4(3\alpha-1)\gamma} \quad \text{for } \alpha < 0. \quad (192)$$

The final result Eq. (165) is obtained from

$$\bar{L}(\tau) = L_0(\tau) + D \langle L_2(\tau) \rangle. \quad (193)$$

D. Simulations and comparison with theory

In this section we present findings that compare simulations of forward stochastic dynamics after target state alignment with theoretical results. The simulations clarify the validity of our small noise approximation close to the target state. Secondly, the simulation results demonstrate the transition between the opaque and transparent regimes in dependence of the γ/D parameter. All shown results have been generated from 20000 trajectories starting at $\tilde{L} = 20$. $D = 0.2$ is held constant.

As noted above and in the main text, the squared coefficient close to the target state serves as an order parameter to distinguish weakly from strongly terminal dynamics. Close to the target state, however, numerical artifacts skew the squared coefficient of variation to higher values. As explained by Ziff et al. [17], those artifacts can be reduced by choosing smaller jump sizes (e.g. smaller noise strength D , smaller simulation stepsize Δt). We therefore chose simulation steps as small as RAM-memory permits to obtain the resolution of the squared coefficient of variation in the main text.

Fig. 14 depicts mean, variance and squared coefficient of variation. For higher values of γ the small noise approximation (SNA) is more valid. For $-1 < \alpha < 0$, the dynamics transitions smoothly between noise dominated and force dominated target state approach.

Fig. 15 shows the mean squared error of C_V^2 which measures the discriminability of dynamics from the pure noise theory and the validity of the small noise approximation. The parameter $\hat{z} = 2\gamma/(D + D\alpha)$ determines the validity of the approximations in both cases. For $\hat{z} \rightarrow 0$ the exact noise theory becomes very accurate, which is for example realized by $D \rightarrow \infty$. On the other hand, for $\hat{z} \rightarrow \infty$ the SNA is a valid approximation of the TSA dynamics, which gets better as $\gamma \rightarrow \infty$ or $\alpha \rightarrow -1$.

VII. A MODEL OF CYTOKINETIC RING CONSTRICTION WITH DISTINCT EFFECTIVE FORCE LAWS

To assess whether TSA ensemble analysis can distinguish different regimes of directed dynamics we here study the exemplary process of Cytokinesis. Cytokinesis is the process of separation of a mother cell into two daughter cells at the end of the cell cycle. For animal cells this separation is driven by a contractile ring formed from actin filaments, myosin and associated proteins. We used a model that describes the contraction and molecular turnover of force generating acto-myosin bundles, i.e. an assembly of filaments and motor complexes[18]. Two coupled differential equations define the model. The first describes how the balance of viscous and elastic forces determines the ring diameter and leads to ring constriction or dilation. The viscous force is written as $-\xi^{-1}\dot{R}$, where $\dot{R}$ denotes the time derivative of the ring radius and ξ an effective friction coefficient. The elastic response of the cell upon cell deformation derives from a harmonic energy term

$$E(R) = \frac{K}{2}(R - R_0)^2 \quad (194)$$

with elastic modulus $K > 0$ and equilibrium radius R_0 . Combined with a term Σ for the contractile stress, we obtain a force balance equation of the form

$$\dot{R} = -\xi \left(\frac{\partial E}{\partial R} + 2\pi\Sigma \right) . \quad (195)$$

The dynamics of the filament concentration $c = N/(2\pi R)$ with N filaments is defined along a ring of length $2\pi R$. Without turnover the ring perimeter therefore changes with $R \propto 1/c$. Including turnover we obtain the material balance equation

$$\dot{c} = k_p - k_d c - \frac{\dot{R}}{R} c \quad (196)$$

with filament polymerization and depolymerization rates k_p and k_d . The contractile stress $\Sigma = AN_b c^2$ models the active force generation of actin filaments and myosin motors. A is the (positively defined) effective material coefficient, N_b the number of distinct filament bundles and c , the number density of filaments per unit length along a bundle. The contractile force is proportional to c^2 to account for the fact that actin filaments need a partner to exert forces. Together Eq. (195) and Eq. (196) define an elementary model of cytokinetic ring constriction.

Zumdieck et. al. used parameters from independent measurements curated from the literature[18]. Comparing numerical solutions of the model, using these parameters with time laps recordings of the first-division constriction dynamics of *C. elegans* oocytes, Zumdieck et. al. found good agreement between model and measurement.

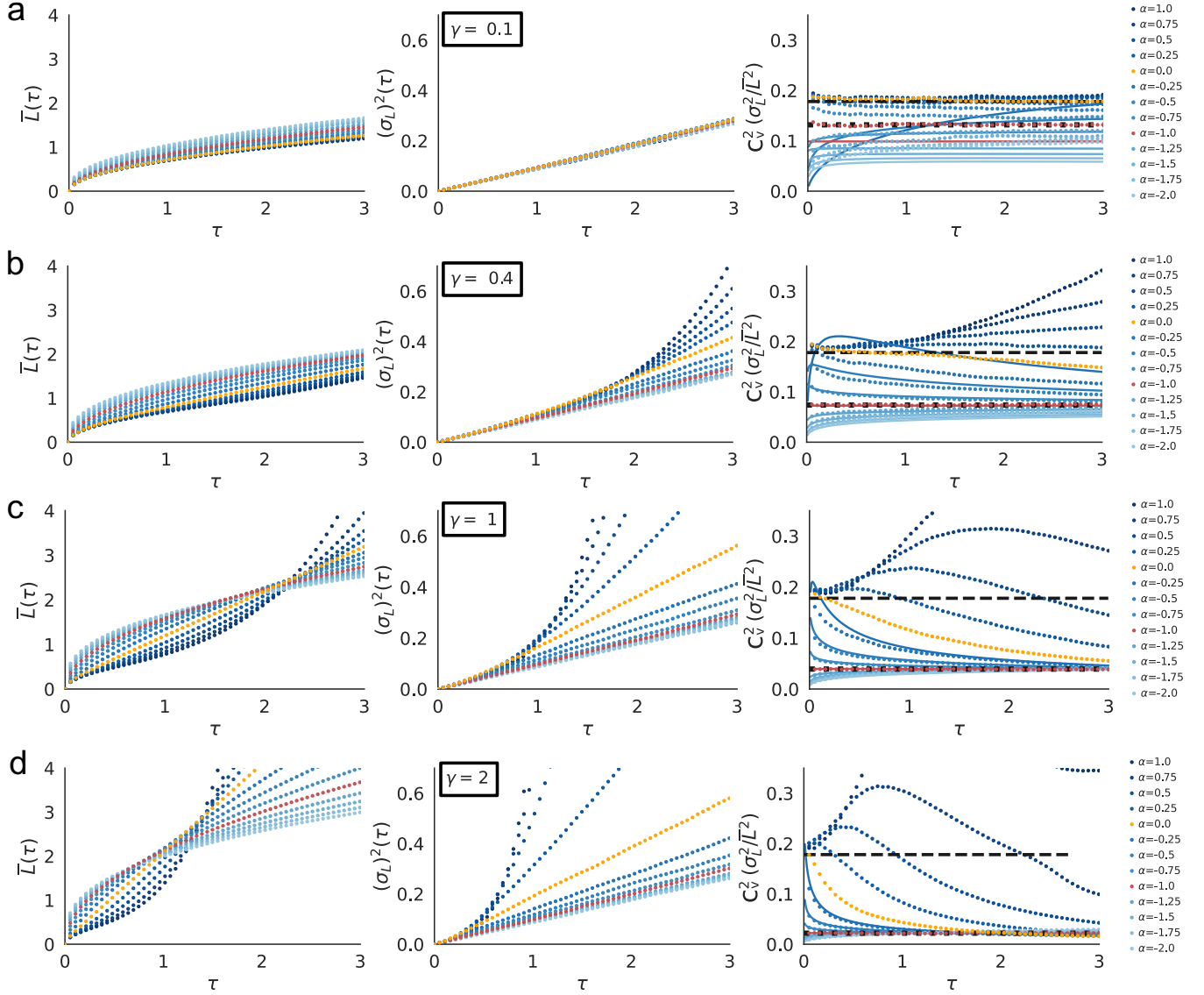


FIG. 14. **TSA ensembles qualitatively differ for weakly and strongly terminal target state approaches which depends on both γ and α .** Dots represent target state aligned forward simulations starting at $\tilde{L} = 20$ and with 20k realizations. From negative α to positive α the colors change from light blue to dark blue. The bounds of the transition regime are marked in red for $\alpha = -1$ and orange for $\alpha = 0$. Small noise approximations are shown as lines with the corresponding color to the simulations. The upper dashed line represents the exact pure noise theory and the lower dashed line represents the exactly solvable $\alpha = -1$ case. **(a)-(d)**: Mean, variance and squared coefficient of variation for different realizations of the parameter $\gamma \in \{0.1, 0.4, 1, 2\}$ and fixed $D = 0.2$. The small noise approximation becomes better for higher values of γ/D .

To allow for different stoichiometries of the potential force generating molecules such as actin and myosin, and to include a stochastic component, we slightly generalized this model dynamics

$$d\tilde{L}(t) = -\left(\gamma_1^\lambda(\tilde{L}(t) - \tilde{L}_m) + \gamma_2^\lambda \hat{c}(t)^n\right) dt + \sqrt{D} dW_t \quad (197)$$

$$d\hat{c}(t) = (k_{\text{on}}^\lambda - k_{\text{off}}^\lambda \hat{c}(t)) dt + \frac{d\tilde{L}(t)}{\tilde{L}(t)} \hat{c}(t). \quad (198)$$

We define $\tilde{L} := R$, $\gamma_1^\lambda := K\xi$, $\tilde{L}_m := R_0$, $\gamma_2^\lambda := 2\pi AN_b$, $k_{\text{on}}^\lambda := k_p$ and $k_{\text{off}}^\lambda := k_d$. To allow for single and pairwise interactions of the force generating molecules we replace the exponent of the concentration by a parameter $n := \{1, 2\}$. In this version, the index $\lambda := \{m, c\}$ further accounts for the possibility to switch between two different regimes. A

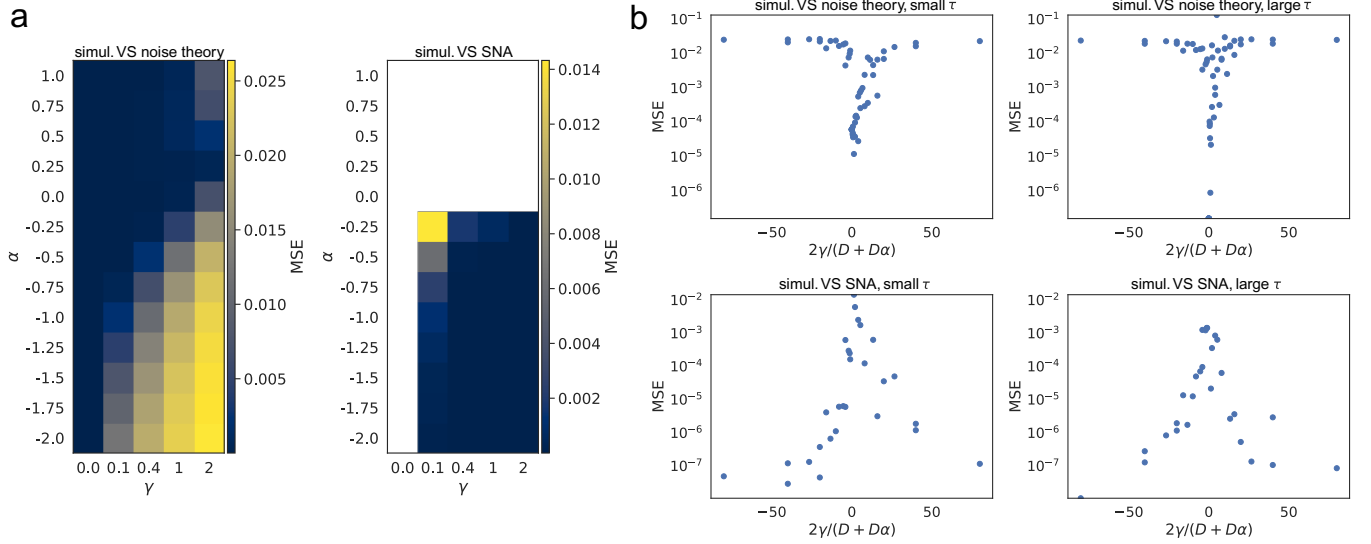


FIG. 15. **Small noise approximation and noise theory (random walk) are valid approximations in different regimes depending on the effective parameter $\hat{z} = 2\gamma/(D + D\alpha)$.** (a): mean squared error (MSE) of the C_V^2 between simulation and exact noise theory as well as small noise approximation (SNA) close to the target state (shown in Fig. 14). The mean squared error was calculated for $\tau \in [0, 1]$. For α around 0 and smaller γ the pure noise theory is a good approximation close to the target state. For larger γ/D and negative α the small noise approximation is valid. (b): mean squared error (MSE) between simulation and exact noise theory as well as between simulation and small noise approximation in dependence of the effective parameter $\hat{z} = 2\gamma/(D + D\alpha)$. Evaluations were termed "small τ " for MSE evaluation for $\tau \in [0, 1]$ and "large τ " for $\tau \in [2, 3]$. For the pure noise theory ($\gamma = 0$) for $\hat{z} \rightarrow 0$ (e.g. with $\gamma/D \rightarrow 0$) the MSE goes to zero and hence shows poor discriminability of those dynamics. The small noise approximation becomes valid for $\hat{z} \rightarrow \infty$ corresponding to $\alpha \rightarrow -1$ or $D \rightarrow 0$, as expected.

maintenance (m) phase where a fixed ring perimeter is stabilized, and a constriction (c) phase where the ring diameter shrinks until cell separation. For simplicity the switching between the two regimes $m \rightarrow c$ is modeled as a discrete shift in parameter space $(\gamma_1^m, \gamma_2^m, k_{\text{on}}^m, k_{\text{off}}^m) \rightarrow (\gamma_1^c, \gamma_2^c, k_{\text{on}}^c, k_{\text{off}}^c)$. Both generalizations, stoichiometries of myosin and stochasticity, were already suggested by the original authors. [18].

Below we show that this generalized model exhibits three qualitatively different biophysically plausible regimes, which can be approximated with a single effective SDE of the form

$$d\tilde{L}(t) = -\gamma_{\text{eff}}\tilde{L}^\alpha + \sqrt{D} dW_t \quad (199)$$

with $\alpha = 0, -1, -2$. These three effective dynamics are recovered from Eq. (197) and Eq. (198), for the biological meaningful limits of fast turnover, stalled myosin turnover, and stalled actin turnover.

A. The fast turnover limit

In the limit of fast turnover ($k_{\text{on}}^\lambda \gg 1$, $k_{\text{off}}^\lambda \gg 1$) and $k_{\text{on}}^\lambda/k_{\text{off}}^\lambda = \text{const.}$, the above model reduces to 1d dynamics of the ring perimeter $\tilde{L}$ which, during the contraction phase, is driven by a constant force γ_{eff} . In this limit $\tilde{c}(t)$ relaxes very fast to its equilibrium concentration $k_{\text{on}}^\lambda/k_{\text{off}}^\lambda$. The remaining SDE for the ring perimeter $\tilde{L}$ is

$$d\tilde{L}(t) = -\left(\gamma_1^\lambda (\tilde{L} - \tilde{L}_m) + \gamma_2^\lambda \left(\frac{k_{\text{on}}^\lambda}{k_{\text{off}}^\lambda}\right)^n\right) dt + \sqrt{D} dW_t. \quad (200)$$

Assuming a very "soft" cell shape and a strong constriction force we set $\gamma_1^c = 0$ and find an equation of the form of Eq. (199). This is the force to deform the entire cell. An analytic expression for the reverse time force close to completion can be obtained using Eq. (118). It turns out that the effect of $\gamma_1 > 0$ on the moments of the aligned reverse time ensemble close to completion is manure. Only the mean changes marginally and rises slightly slower than in the case with $\gamma_1 = 0$.

B. Stalled turnover limits

In the limit of stalled turnover ($k_{\text{on}}^\lambda \approx 0$, $k_{\text{off}}^\lambda \approx 0$) all force generating molecules are trapped in the ring over the time scale of the constriction phase. We thus set k_{on}^c and k_{off}^c to zero. The concentration dynamics from Eq. (198) and during constriction then reduces to

$$\frac{d(\widehat{c}(t)\widetilde{L}(t))}{dt} = \dot{\widehat{c}}(t)\widetilde{L}(t) + \widehat{c}(t)\dot{\widetilde{L}}(t) = 0, \quad (201)$$

implying a fixed number of force generating molecules on the ring. In this limit

$$\widehat{c}(t)\widetilde{L}(t) = \text{const.} \quad (202)$$

As this is maintained during constriction, the constant value is inherited from the value of this product at the end of the maintenance phase, the switching time t_{sw} . We can therefore replace $\widehat{c}(t)$ in the perimeter dynamics Eq. (197), and obtain

$$d\widetilde{L}(t) = - \left(\gamma_1^c (\widetilde{L} - \widetilde{L}_m) + \gamma_2^c \left(\frac{\overline{\widehat{c}(t_{\text{sw}})\widetilde{L}(t_{\text{sw}})}}{\widetilde{L}(t)} \right)^n \right) dt + \sqrt{D} dW_t \quad (203)$$

with $\overline{\widehat{c}(t_{\text{sw}})}$ approximated by the ratio of $k_{\text{on}}^m/k_{\text{off}}^m$ and

$$\overline{\widetilde{L}(t_{\text{sw}})} = \widetilde{L}_m - \frac{\gamma_2^m}{\gamma_1^m} \overline{\widehat{c}(t_{\text{sw}})}, \quad (204)$$

where $\overline{\widehat{c}(t_{\text{sw}})}$ and $\overline{\widetilde{L}(t_{\text{sw}})}$ are the average values during the maintenance phase. For the example displayed in the main text, we again assume dominance of the constriction force ($\gamma_1^c = 0$) during the constriction phase. Note that, as the concentration of force generating molecules diverges, this is a particular mild assumption here. The effective dynamics then terminates either $\propto 1/\widetilde{L}$ or $\propto 1/\widetilde{L}^2$ depending on the model variants ($n = 1$: myosin; $n = 2$: actin) for the force generating molecule.

C. Simulations

Sample paths for the three different constriction scenarios with constriction forces constant ($\alpha = 0$), proportional to $\propto 1/\widetilde{L}$ ($\alpha = -1$) or $\propto 1/\widetilde{L}^2$ ($\alpha = -2$) were generated from Eq. (197) and Eq. (198). All simulations were started from the equilibrium distribution of the maintenance phase. After a time t_{sw} (chosen larger than the window used for inference), the dynamics for each sample path was switched to the constriction regime. The case corresponding to $\alpha = -1$ is provided in Fig. 6 of the main text. Here we additionally display the two cases with $\alpha = 0, -2$ (see Fig. 16). Tab.I lists the parameter settings for all simulations. For integration we used a standard Euler scheme with

Parameters	Simulation 1 ($\alpha = 0$)		Simulation 2 ($\alpha = -1$)		Simulation 3 ($\alpha = -2$)	
	maintenance	constriction	maintenance	constriction	maintenance	constriction
n	1	1	1	1	2	2
$k_{\text{on}}/\mu\text{m s}^{-1}$	400	2000	0.5	0	0.7	0
$k_{\text{off}}/\text{s}^{-1}$	10	20	0.01	0	0.1	0
γ_1/s^{-1}	0.075	0	0.075	0	0.075	0
$\gamma_2/\mu\text{m}^{1+n} \text{s}^{-1}$	$2\pi \cdot 3.6 \cdot 10^{-5}$	$2\pi \cdot 3.6 \cdot 10^{-5}$	$2\pi \cdot 3.6 \cdot 10^{-5}$	$2\pi \cdot 3.6 \cdot 10^{-5}$	$2\pi \cdot 3.6 \cdot 10^{-5}$	$2\pi \cdot 3.6 \cdot 10^{-5}$
$\widetilde{L}_m/\mu\text{m}$	14.5	14.5	14.5	14.5	14.5	14.5
$D/\mu\text{m}^2 \text{s}^{-1}$	0.04	0.04	0.04	0.04	0.04	0.04

TABLE I. **Parameter settings used for 3 different sample path ensembles created from Eq. (197) and Eq. (198).** Simulation 2 is discussed in the main text.

time step $\Delta t = 0.05\text{s}$.

D. Path inference

To infer the most likely constriction scenario hidden in each of the forward simulations as defined in Table I, we maximize the path likelihood of the respective ensemble after alignment and time reversion. We implement the approach discussed in section VIII using Nested Sampling[19], which yields maximum posterior estimates for the parameters and a direct estimate of the Bayesian model evidence. We infer the reverse time force from the TSA ensemble and reconstruct the underlying forward force. We assumed the forward force law is of power law form $f(\tilde{L}) = -\gamma\tilde{L}^\alpha$. We can therefore directly read off the forward force $f(L)$ from the inferred reverse time force $f^{\text{TSA}}(L)$.

For each of the three simulations defined in Table I the inference procedure is identical. We here discuss Simulation 2 (with true effective $\alpha = -1$) shown in the main text. The idea is to treat the simulation data as black box, as experimental data would be, and determine which forward force law $f(\tilde{L})$ is most suitable to describe the constriction dynamics. In principle the maximal included lifetime of the reverse time trajectories $N\Delta\tau$ should be optimized as well. Starting from very short trajectories for which contributions of the maintenance phase are negligible, and increasing the length until distinctions from a pure ensemble become detectable, then marks the transition from constriction to maintenance. We here, for simplicity, directly choose N based on visual inspection of the aligned reverse time ensemble.

There are two options to find the best model. First, to simultaneously optimize for $\alpha, \gamma_{\text{eff}}, D$. Second to choose one α from the three above described mechanisms, assuming it contains the correct model, and infer the best fitting γ_{eff}, D . With the first approach we find the best model with its maximum posterior parameters. With the latter we find the best fitting parameters for each of the candidates ($\alpha = 0, -1, -2$). This then allows to quantitatively compare the three different models either in terms of the Bayesian evidence or, in terms of their moments which we each calculate from simulations of the respective reverse time SDE Eq. (120) using the newly inferred parameter $\gamma_{\text{MAP}}, D_{\text{MAP}}$.

For Simulation 2 (with true effective $\alpha = -1$) the results of this comparison are shown in Fig. 6 of the main text. For the “true” case $\alpha = -1$, the full terminal aligned simulation and the inferred dynamics perfectly coincide in their moments. For $\alpha = 0, -2$ they strongly deviate. A similar observation holds for Simulation 1 and 3 shown in Fig. 16. For both, the correct dynamics are recovered while the deviant models can not be matched in their statistics. In total this shows that our path ensemble inference approach for reverse time analysis allows to reliably infer the correct underlying mechanism while rejecting deviant models. The theory of TSA ensemble inference thus provides a reliable framework for the inference of effective dynamics.

VIII. REVERSE-TIME ENSEMBLE PATH INFERENCE

The reverse time TSA ensemble approach aims at the inference of the underlying forward dynamics from dynamics with identifiable dynamics only close to the target state. We here propose to directly infer the reverse time force $f^{\text{TSA}}(L)$ from TSA sample paths using a path-ensemble-likelihood inference scheme.

The construction idea of this likelihood inference scheme follows classical maximum likelihood and Bayesian path inference approaches[20–26]. We first define the transition probability density for discrete sample paths starting at L_{TS} at time $\tau = 0$ and ending at τ_f for simplicity. Sample points are taken with equal spacing $\Delta\tau$. We considering sample paths of duration $T = N\Delta\tau$. The transition probability density for individual realizations of such a Markovian process reads

$$P(L_f, \tau_f | L_{\text{TS}}, 0) = \prod_{i=0}^{N-1} P(L_{i+1}, \tau_{i+1} | L_i, \tau_i) . \quad (205)$$

Assuming individual, statistically independent sample paths, the total likelihood of a finite size sample n_{ens} of sample paths is the product of individual transition probabilities. Taking the logarithm the log likelihood function is

$$\log \mathcal{L} = \sum_{j=1}^{n_{\text{ens}}} \sum_{i=0}^{N-1} \log P(L_{i+1}^{(j)}, \tau_{i+1} | L_i^{(j)}, \tau_i) \quad (206)$$

which can be used for maximum likelihood inference of model parameter. The exact transition probability density $P(L_{i+1}, \tau_{i+1} | L_i, \tau_i)$ is not available analytically for most stochastic processes. A simple approximation for $P(L_{i+1}, \tau_{i+1} | L_i, \tau_i)$ useful for closely sampled trajectories is of Gaussian form

$$P(L_{i+1}, \tau_{i+1} | L_i, \tau_i) = \frac{1}{\sqrt{2\pi D\Delta\tau}} e^{-\frac{(L_{i+1} - L_i - f^{\text{TSA}}(L_i)\Delta\tau)^2}{2D\Delta\tau}} . \quad (207)$$

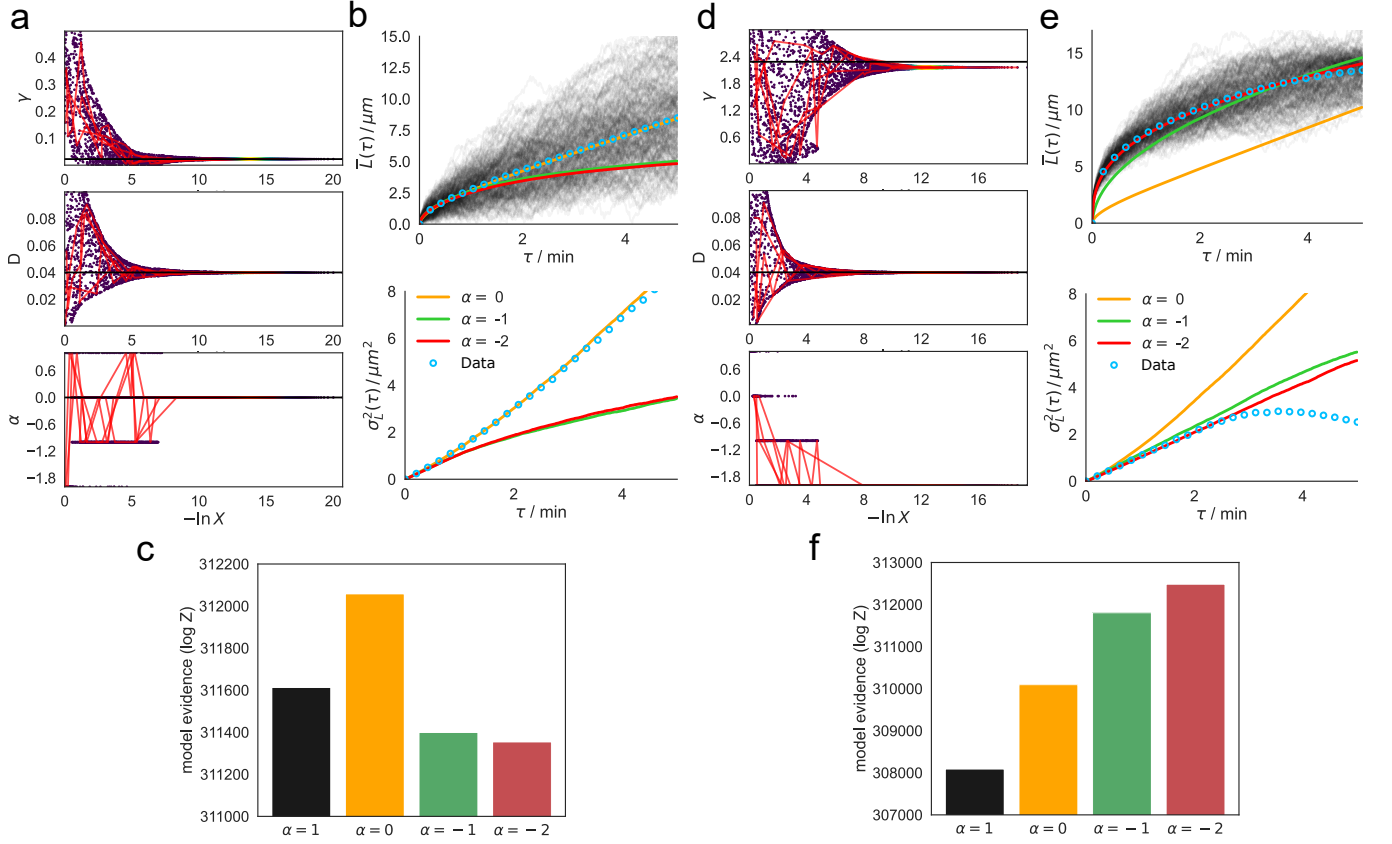


FIG. 16. **The dynamical law leading to constriction can unambiguously be inferred from realizations of the Zumdieck model, using Bayesian path integral inference Eq. (208).** (a): We confirm the inferred underlying force law $f(\tilde{L})$ by showing the nested sampling results for the advection case $\alpha = 0$, which converge to the true parameter values. (b): Given the correct underlying force law $f(\tilde{L}) = -\gamma$ ($\alpha = 0$), and inferring optimal parameters γ and D , only the case $\alpha = 0$ (yellow line) predicts both the mean and variance of the Zumdieck model (blue circles). (c): The log-evidence for each model singles out the correct model and therefore demonstrates that inference of the advection scenario can be performed. (d): We confirm the inferred underlying force law $f(\tilde{L})$ by showing the nested sampling results for the case $\alpha = -2$, which converge to the true parameter values. γ is slightly underestimated because we performed inference “too far” from the target state, as can also be seen in (d). (e): Given the correct underlying force law $f(\tilde{L}) = -\frac{\gamma}{L^2}$ ($\alpha = -2$), and inferring optimal parameters γ and D , only the case $\alpha = -2$ (red line) predicts both the mean and variance of the Zumdieck model (blue circles) close to the target state. (f): The log-evidence for each model confirms that the correct model $\alpha = -2$ was inferred from the simulated trajectories of the cytokinesis model.

This is equivalent to a first order stochastic simulation of an SDE in Ito interpretation, where the change dL with respect to the deterministic force times $\Delta\tau$ plus a random step with zero mean and variance $D\Delta\tau$ is evaluated. The log-likelihood under the approximation of Gaussian transition probabilities thus reads

$$\log \mathcal{L} = \sum_{j=0}^{n_{\text{ens}}} \sum_{i=0}^{N-1} \left(-\frac{\left(L_{i+1}^{(j)} - L_i^{(j)} - f^{\text{TSA}}(L_i^{(j)})\Delta\tau \right)^2}{2D\Delta\tau} - \frac{1}{2} \log(2\pi D\Delta\tau) \right). \quad (208)$$

This approximation becomes exact for small time steps, and deviations occur as the time-steps become bigger. It is therefore recommended to check after optimization, if the residual increments after subtraction of the deterministic part are actually Gaussian. If not, more sophisticated path inference techniques can be used[27–29], which can cope with “almost” Gaussian transition probabilities[30, 31] or even arbitrary step size[32].

For forward power law forces of the form $f(L) = -\gamma L^\alpha$, and close to the target state, the corresponding reverse time forces $f^{\text{TSA}}(L) = f(L) + f^A(L)$ can be stated exactly using Eq. (120) for the free energy force $f^A(L)$. Using $f^A(L)$, in the form as defined in Eq. (120), the log-likelihood is not easily evaluated numerically for small L . As both $\Gamma(\nu)$, $\Gamma(\nu, z)$ and $\exp(z)$ need to be evaluated numerically and separately, slight inconsistencies can lead to numerical

instabilities. We therefore transformed $f^{\mathcal{A}}(L)$ to forms in which only one special function is evaluated numerically. This is feasible when treating $\alpha < -1$ and $\alpha > -1$ separately. The full free energy force then splits into three cases

$$f^{\mathcal{A}}(L) = \begin{cases} \frac{D}{-\frac{2L^{\alpha+1}\gamma}{\alpha D + D} {}_1F_1(1; 1 + \frac{1}{1+\alpha}; -\frac{2L^{\alpha+1}\gamma}{\alpha D + D})} & \text{for } \alpha > -1 + \epsilon \\ \frac{2\gamma}{L} - \frac{\alpha D}{L} & \text{for } -1 + \epsilon < \alpha < -1 - \epsilon \\ \frac{-D(1+\alpha)}{-\frac{2L^{\alpha+1}\gamma}{\alpha D + D} U(1; 1 + \frac{1}{1+\alpha}; -\frac{2L^{\alpha+1}\gamma}{\alpha D + D})} & \text{for } -1 - \epsilon < \alpha < -1 - \epsilon. \end{cases} \quad (209)$$

In our experience this representation with $\epsilon = 0.05$ worked robustly. Here ${}_1F_1(a; b; z)$ is the Kummer confluent hypergeometric function, $U(a; b; z)$ is Tricomi's confluent hypergeometric function. To obtain this representation we used the substitutions

$$\Gamma(a) - \Gamma(a, z) = a^{-1} z^a e_1^{-z} F_1(1; 1 + a; z) \quad (210)$$

which can be derived from from Abramovitz & Stegun (AS 6.5.3) and (AS 6.5.12)[13], and

$$\Gamma(a, z) = z^a U(1; 1 + a; z) e^{-z} \quad (211)$$

which follows from Abramovitz & Stegun (AS 13.1.29) and (AS 13.6.28)[13]. We point out, that $f^{\text{TSA}}(L(\tau_0))$ diverges for $L(\tau_0) = L_{\text{TS}}$. We therefore leave the target state data point out and start the inference with the next or second next state.

On a practical note, evaluations of the likelihood functions are numerically much faster when, for a specific α , a simplified version of the force can be obtained. The hypergeometric functions are generally numerically unstable for $\alpha < -1$, which means that many terms of the series have to be calculated to obtain reasonable accuracy. This results in evaluations of the path likelihood function which are very time consuming. Hence, it is advised that the practitioner obtains a functional form without hypergeometric function for specific models wherever possible.

The strength of the path ensemble inference formalism compared to optimizing predicted moments such as mean and variance is, that the optimization is performed with respect to the full likelihood. No considerations about sufficient statistics or how to weigh the different moments relative to each other in a loss function are required. By directly inferring the underlying reverse time SDE, mean, variance etc. become predictions. The comparison between observed and predicted moments can then be used to test the inference and accept or reject the model. As described in the main text, we made an explicit comparison of the path inference scheme with the method of moments, also called *ensemble method*.

In the *ensemble* strategy, model accuracy is evaluated via the residuals between empirical ensemble mean and model mean $R_{\mu,i} = x_i - \bar{L}(\tau_i)$ and similar for the variance $R_{\sigma,i} = y_i - \sigma_L^2(\tau_i)$. x_i, y_i are the data derived empirical mean and variance at times τ_i . The model moments can be obtained from numerical simulations, exact analytical calculations or our above-derived small noise theory. The loss function reads

$$\mathcal{L} = - \sum_{i=1}^{N_\tau} (R_{\mu,i}^2 + R_{\sigma,i}^2). \quad (212)$$

We performed inference of model parameters for the Bessel case with the underlying force law $f(\tilde{L}) = -\frac{\gamma}{\tilde{L}}$ ($\alpha = -1$) and varied the data quality by subsampling from the full ensemble. By sampling we mean that we varied the number of trajectories N_{ens} per inference run and the number time steps per trajectory N_t . For each fixed N_{ens} and N_t , the inference was repeated 200 times by subsampling N_{ens} trajectories from a large ensemble containing 50 000 trajectories in total. The number and location of the subsampled time steps was not changed.

In Fig. 17, those results are summarized by showing the accuracy, the squared distance of the mean inferred parameter compared to the real parameter, and the precision, which is the standard deviation of the inferred parameters. The accuracy therefore shows whether the inference is unbiased in the limit of many inferences, while the precision is a measure for the expected spread. Reliable inference can only occur for both high accuracy and precision.

These results show that the ensemble method can produce reliable parameter inference in the high number of trajectories limit $N_{\text{ens}} \gg 1$. Additionally, it can be seen that the ensemble method only depends on those and strikingly not on the number of subsampled time steps N_t . This method is therefore recommended when the sampling rate of single experiments is too high to obtain Gaussian transition probabilities, which would enable reliable path inference.

On the other hand, the path method produces reliable inference of D for even only 2 trajectories if the sampling rate is high enough. The precision for the inference of γ is only high if there are enough trajectories.

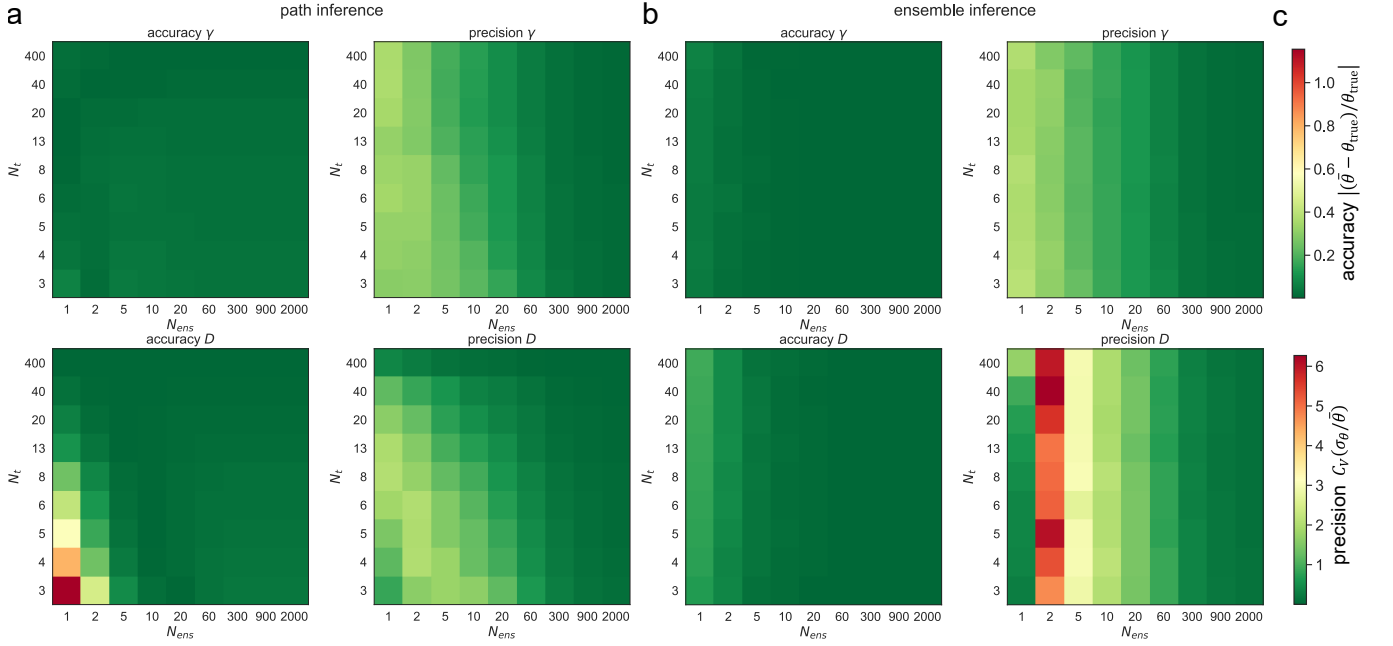


FIG. 17. **Phasediagrams of inference accuracy and precision.** We show the accuracy and precision of 200 inference runs subsampled from an ensemble of 50000 trajectories. To obtain accuracy we calculated the relative distance between the mean of the inferred parameters and the true parameters $|(\bar{\theta} - \theta_{\text{true}})/\theta_{\text{true}}|$. The precision is obtained as the coefficient of variation $C_V = \sigma_{\theta}/\bar{\theta}$ of the distribution of inferred parameters. On the abscissa the number of trajectories per inference run N_{ens} is displayed and on the ordinate the number of time steps per trajectory N_t . The colorscale for all accuracy results and for all precision results is the same respectively. **(a):** Results for path inference. First row is displaying results for γ and second row for D . **(b):** Results for ensemble inference. First row is displaying results for γ and second row for D . **(c):** Colorscales for all accuracy values (top) and precision values (bottom).

A. Accounting for measurement noise

In case of homogeneous Gaussian noise, there is a simple extension for the path-based likelihood that simultaneously infers the measurement noise from the data, together with the parameters. The log-likelihood under this assumption then reads

$$\log \mathcal{L} = \sum_{j=1}^{n_{\text{ens}}} \sum_{i=0}^{N-1} \left(-\frac{\left(L_{i+1}^{(j)} - L_i^{(j)} - f^{\text{TSA}}(L_i^{(j)}) \Delta\tau \right)^2}{2D\Delta\tau + 2\sigma_{\text{meas}}^2} - \frac{1}{2} \log(2\pi(D\Delta\tau + \sigma_{\text{meas}}^2)) \right). \quad (213)$$

where σ_{meas} is the standard deviation of an additive Gaussian measurement error with zero mean. σ_{meas} would constitute an additional parameter during inference.

-
- [1] C. W. Gardiner, Handbook of stochastic methods for physics, chemistry and the natural sciences, vol. 13 of, Springer series in synergetics (1985).
 - [2] S. N. Majumdar and H. Orland, Effective langevin equations for constrained stochastic processes, Journal of Statistical Mechanics: Theory and Experiment **2015**, P06039 (2015).
 - [3] B. D. O. Anderson, Reverse-time diffusion equation models, Stochastic Processes and their Applications **12**, 313 (1982).
 - [4] I. M. Sokolov, Statistical mechanics of entropic forces: disassembling a toy, European Journal of Physics **31**, 1353 (2010).
 - [5] U. Seifert, Entropy production along a stochastic trajectory and an integral fluctuation theorem, Physical review letters **95**, 040602 (2005).
 - [6] H. Föllmer, Time reversal on wiener space, in *Stochastic Processes in Mathematics and Physics* (Springer, 1986) pp. 119–129.
 - [7] G. Wilemski and M. Fixman, General theory of diffusion-controlled reactions, The Journal of chemical physics **58**, 4009 (1973).

- [8] D. Holcman, A. Marchewka, and Z. Schuss, Survival probability of diffusion with trapping in cellular neurobiology, *Physical Review E* **72**, 031910 (2005).
- [9] Z. Schuss, *Brownian dynamics at boundaries and interfaces* (Springer, 2015).
- [10] R. Erban and S. J. Chapman, Reactive boundary conditions for stochastic simulations of reaction–diffusion processes, *Physical Biology* **4**, 16 (2007).
- [11] Q. Zhang, J. Brujić, and E. Vanden-Eijnden, Reconstructing free energy profiles from nonequilibrium relaxation trajectories, *Journal of Statistical Physics* **144**, 344 (2011).
- [12] A. J. Bray, Random walks in logarithmic and power-law potentials, nonuniversal persistence, and vortex dynamics in the two-dimensional xy model, *Physical Review E* **62**, 103 (2000).
- [13] M. Abramowitz and I. A. Stegun, *Handbook of mathematical functions: with formulas, graphs, and mathematical tables*, Vol. 55 (Courier Corporation, 1964).
- [14] E. Martin, U. Behn, and G. Germano, First-passage and first-exit times of a besell-like stochastic process, *Physical Review E* **83**, 051115 (2011).
- [15] S. Redner, *A guide to first-passage processes* (Cambridge University Press, 2001).
- [16] L. M. Ricciardi and S. Sato, First-passage-time density and moments of the ornstein-uhlenbeck process, *Journal of Applied Probability* **25**, 43 (1988).
- [17] R. M. Ziff, S. N. Majumdar, and A. Comtet, Capture of particles undergoing discrete random walks, *The Journal of chemical physics* **130** (2009).
- [18] A. Zumdick, K. Kruse, H. Bringmann, A. A. Hyman, and F. Jülicher, Stress generation and filament turnover during actin ring constriction, *PloS one* **2**, e696 (2007).
- [19] J. Skilling, Nested sampling, Bayesian inference and maximum entropy methods in science and engineering **735**, 395 (2004).
- [20] M. El Beheiry, M. Dahan, and J.-B. Masson, Inferencemap: mapping of single-molecule dynamics with bayesian inference, *Nature methods* **12**, 594 (2015).
- [21] J.-B. Masson, P. Dionne, C. Salvatico, M. Renner, C. G. Specht, A. Triller, and M. Dahan, Mapping the energy and diffusion landscapes of membrane proteins at the cell surface using high-density single-molecule imaging and bayesian inference: application to the multiscale dynamics of glycine receptors in the neuronal membrane, *Biophysical journal* **106**, 74 (2014).
- [22] S. Tuerkcan, A. Alexandrou, and J.-B. Masson, A bayesian inference scheme to extract diffusivity and potential fields from confined single-molecule trajectories, *Biophysical journal* **102**, 2288 (2012).
- [23] J.-B. Masson, M. Dahan, and A. Triller, Pitfalls in the quantitative analysis of random walks and the mapping of single-molecule dynamics at the cellular scale, *arXiv preprint arXiv:1502.07285* (2015).
- [24] C. Dargatz, *Bayesian inference for diffusion processes with applications in life sciences*, Ph.D. thesis, lmu (2010).
- [25] G. B. Durham and A. R. Gallant, Numerical techniques for maximum likelihood estimation of continuous-time diffusion processes, *Journal of Business & Economic Statistics* **20**, 297 (2002).
- [26] A. S. Hurn, J. Jeisman, and K. A. Lindsay, Seeing the wood for the trees: A critical evaluation of methods to estimate the parameters of stochastic differential equations, *Journal of Financial Econometrics* **5**, 390 (2007).
- [27] T. Ozaki, Statistical identification of storage models with application to stochastic hydrology 1, *JAWRA Journal of the American Water Resources Association* **21**, 663 (1985).
- [28] M. Kessler, Estimation of an ergodic diffusion from discrete observations, *Scandinavian Journal of Statistics* **24**, 211 (1997).
- [29] O. Elerian *et al.*, A note on the existence of a closed form conditional transition density for the milstein scheme, *Economics discussion paper* , W18 (1998).
- [30] Y. Aït-Sahalia, Maximum likelihood estimation of discretely sampled diffusions: a closed-form approximation approach, *Econometrica* **70**, 223 (2002).
- [31] Y. Ait-Sahalia *et al.*, Closed-form likelihood expansions for multivariate diffusions, *The Annals of Statistics* **36**, 906 (2008).
- [32] A. Beskos, O. Papaspiliopoulos, G. O. Roberts, and P. Fearnhead, Exact and computationally efficient likelihood-based estimation for discretely observed diffusion processes (with discussion), *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* **68**, 333 (2006).