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CRITICAL SWITCHING BEHAVIOUR IN SPARSELY POPULATED SYSTEMS

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The basic kinematic behaviour of a threshold switch in a system with a sparse population is investigated. We determine the basic quantities such as the number probability density function, the survival probability, the characteristic switching time, and the response to external triggering of the switch. The modelling approach is then extended to systems with response retardation, which, it is argued, may improve the stability of the switch.

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1. Introduction

The human body comprises a large variety of different cell types. At the same time, (almost) all of these cells share the same genetic material. The diversity comes about by a control mechanism (regulation) which decides which subset of all the available genes are actually expressed within one given cell during the processes of transcription and translation.[1] Gene regulation is, in turn, controlled by the particular chemistry within the cell, i.e. the presence or absence of certain regulatory proteins or other molecules; the co-operative action of all ingredients determines at which point on the DNA (promoter site) a given protein transcription factor binds. Subsequently, an RNA polymerase binds to the complex of transcription factors and proceeds along the DNA, to evaluate the genetic code of the associated gene.[2]

Gene regulation is part and parcel of biological evolution and development. One of the best studied examples of such a regulatory mechanism is the genetic switch associated with the life cycle of *Escherichia coli* bacteria which have been infected by bacteriophage λ, i.e. the λ-switch.[3] When phage λ enters the *E. coli* cell, it fuses its DNA into the (much longer) DNA of its host. The binding of either repressor or promoter on certain operator sites determines which gene, to the left or to the right of these operator sites, is expressed. This decision is called a genetic switch,

and its state determines the future fate of the cell: if repressor(s) bind(s), a gene is transcribed which causes the production of repressor molecules in the host cell's chemical facilities such that the system locks onto the inert (dormant) lysogenic state; otherwise, the opposite gene stimulates the production of new λ-phages, ultimately lethal to the host cell (lysis). The λ-switch can flip from the lysogenic to the lysis-pathway through external stimulus (e.g. UV light cleaving the repressor dimers, or a starving host), or through *fluctuations*.[1–3]

λ-repressor acts co-operatively: one repressor dimer already bound facilitates the binding of a second, and flipping the switch requires the dissociation of both dimers from the DNA. In contrast, the Lac operon, which regulates the expression of a gene which prompts production of an enzyme which can process lactose in the absence of glucose, is controlled by a single repressor molecule and/or a single promoter (activator).[2]

Biological cells combine the interesting properties of being a fluctuation-dominated (Brownian) system, and using comparatively small numbers of messenger molecules such as above-described repressor molecules, in an apparently delicate systems of (co-operative) checks and balances.[4] Thus, biological switches differ considerably from molecular switches, i.e. chemical molecules being synthesised in the emerging field of topochemistry, a branch of organic chemistry.[5] There, a single molecule possesses mechanically linked subunits which can attain two different positions within the molecule, such as the ring unit in rotaxanes. Such molecular switches can be *externally controlled* energetically and entropically,[6,7] i.e. through coupling to a macroscopic bath.

In what follows, we develop a basic picture for biological switches based on the threshold model presented in Ref. 8. To this end, we note that in large enough systems the dynamics of a population is usually described in the continuum limit in terms of the rate equation[9]

$$\frac{d\phi(t)}{dt} = k_0 + k_1\phi(t)\,, \tag{1}$$

which describes the time-evolution of the "concentration" $\phi(t)$, a macroscopic quantity. In Eq. (1), the parameters k_i represent the rate constants of dimension $[k_i] = \sec^{-1}$, which can either be independent or proportional to the quantity $\phi(t)$. The rate equation (1) does not provide any information about the fluctuations of the quantity ϕ. Such fluctuations, usually being of the order of the square root of the constituents of the system, can be neglected in large systems. Conversely, if only a small population is considered, a more fundamental description is necessary. A good basis is the (difference-differential) master equation[10]

$$\frac{\partial P(n,t)}{\partial t} = (\mathbb{E}^{-1} - 1)G(n)P(n,t) + (\mathbb{E} - 1)R(n)P(n,t) \tag{2}$$

where $\mathbb{E}^{\pm}P(n,t) \equiv P(n \pm 1, t)$. G and R refer to the **G**eneration and **R**emoval of particles the number of which is measured by n.[11] The master equation (2) includes

the details of the diffusion in n-space, and therefore offers the possibility to calculate all moments and correlations.

In the following, we formulate a simple immigration-death (ID) model from which we derive certain measures for biological switches, based on the threshold model. From the survival probability for simple and co-operative switches, we obtain estimates for the characteristic switching times. By making use of a generalized Laplace transform, we can infer generalizations of these measures to systems which exhibit a time lag in their response, or even a long-tailed memory.

2. Formulation of the Model

A sufficient model for a simple biological switch is the (discrete) ID-process, in which the population of messenger molecules n is changed by degradation with rate k_d and by immigration with rate k_i.[4,8] In the following, we assume $k_i, k_d \geq 0$. The associated master equation

$$\frac{\partial P(n,t)}{\partial t} = k_i P(n-1,t) + k_d(n+1)P(n+1,t) - (k_i + k_d n)P(n,t) \tag{3}$$

ensures that $P(n,t) = 0$ for all $n < 0$ by the n-proportionality of the death term.[10,11] If time is measured in inverse units of k_d and we define $\varphi \equiv k_i/k_d$, we can rescale Eq. (3) to obtain

$$\frac{\partial P(n,t)}{\partial t} = \varphi P(n-1,t) + (n+1)P(n+1,t) - (\varphi + n)P(n,t)\,. \tag{4}$$

The mean number $\langle n(t)\rangle$, predicted by Eq. (3), is

$$\langle n(t)\rangle = me^{-t} + \varphi(1-e^{-t})\,, \tag{5}$$

which combines an exponential decay of the initial distribution with m molecules and an immigration term. Note that the equation for $\langle n(t)\rangle$ corresponds to the rate equation for ϕ. The variance $\mathrm{var}(t) \equiv \langle (n(t) - \langle n(t)\rangle)^2\rangle$ of the process is given by

$$\mathrm{var}(t) = m(1-e^{-t})e^{-t} + \frac{\varphi}{2}(1-e^{-2t}) + (e^{-2t} - 2e^{-t} + 1)\,. \tag{6}$$

In the stationary state ($\lim_{t\to\infty}$), the mean number and variance converge to

$$\langle n_\infty\rangle = \varphi\,, \tag{7}$$

$$\mathrm{var}_\infty = \varphi\,, \tag{8}$$

i.e. the standard deviation equals $\sqrt{n_\infty}$.

The general solution of the master equation (3) for the probability density function P with initial condition $P_0(n) = \delta_{n,m}$ reads[12]

$$P(n,t|m,0) = e^{-\varphi(1-e^{-t})} \sum_{k=0}^{\min\{m,n\}} \binom{m}{k} e^{-kt}(1-e^{-t})^{m+n-2k} \frac{\varphi^{n-k}}{(n-k)!}\,. \tag{9}$$

With the property $\binom{m}{k} = 0$, $\forall k > m$ and $(n-k)! \to \infty$, $\forall k \geq n$, this expression can actually be rewritten in terms of a confluent hypergeometric function.[8] The time

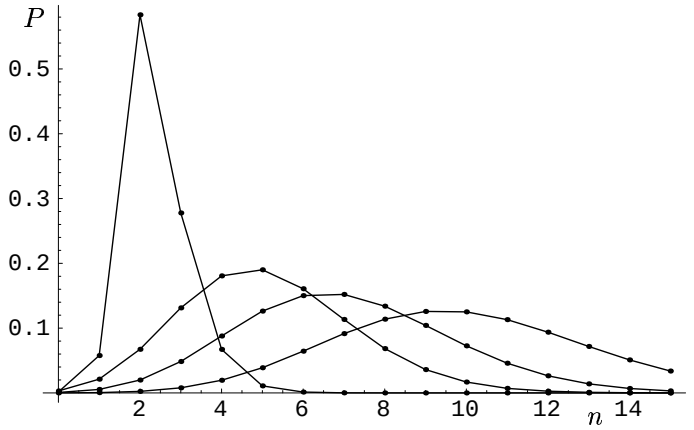

Fig. 1. Probability density function $P(n,t|2,0)$ for successive times: $t = 0.05$, 0.5, 1, 5. The lines connect the points of P, and are only meant to guide the eye. Note the rather broad distribution for longer times.

evolution of the probability density function is shown in Fig. 1. The stationary behaviour of the ID-process

$$P_{\rm st}(n) = e^{-\varphi}\frac{\varphi^n}{n!} \tag{10}$$

corresponds to a Poisson distribution.

3. Threshold Definition and Survival Probability

Disregarding the exact subtleties of a biological switch, we can abstract it by saying that the system remains in a "good" state if at least a critical number $n_{\rm crit}$ of molecules is present. This can be the number of molecules within the entire host cell as in the more traditional model for switches which include the well-stirredness assumption,[3,13,14] or within the reaction volume in the space-dependent switch model proposed in Ref. 4. If less than $n_{\rm crit}$ molecules are present, the system is assumed to turnover to a different "fatal" state, i.e. the switch has flipped. This simplest version of a switch does not involve co-operativity.

Above phenomenological behaviour can be modelled by an absorbing boundary at $\bar{n} \equiv n_{\rm crit} - 1$, so that all states of the system which are above-critical (good) are counted in the survival function. The solution of the master equation (3) which corresponds to this boundary value problem can be constructed with the method of images, to produce

$$Q(n,t|m,0|\overline{n}) = P(n,t|m,0) - P(2\overline{n}-n,t)\,. \tag{11}$$

Thus, the amount of probability which has leaked out (has touched the absorbing boundary) is subtracted from the original density function. This method is illustrated in Fig. 2.

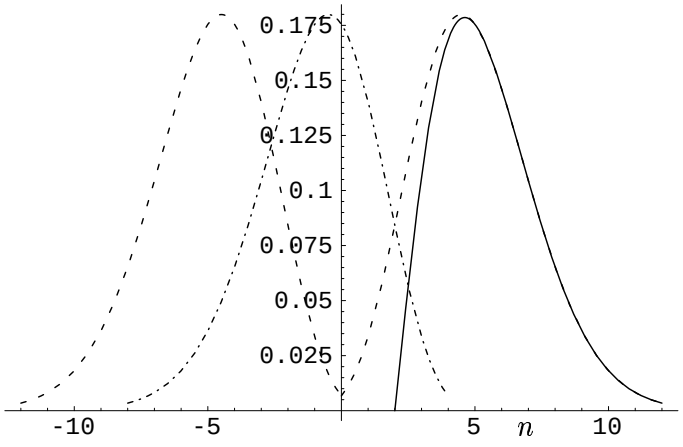

Fig. 2. Illustration of the method of images for the stationary probability density function $P_{\rm st}(n)$. Dashed lines: Original, unbounded probability density $P_{\rm st}(n)$, and its mirror, reflected in the ordinate. Point-dashed: Mirrored function, shifted by $2\overline{n}$. The point-dashed and the original functions overlap. The part which has hit the absorbing boundary ($\overline{n} = 2$) corresponds to the overlap with the point-dashed line, and is subtracted from the original function, to produce the full line, the image solution Q.

From the boundary value solution Q, one obtains the survival function

$$\mathcal{S}(t) \equiv \sum_{n_{\rm crit}}^{\infty} Q(n, t|m, 0|\bar{n}) \tag{12}$$

which measures the probability that the system is in the good state. The complementary quantity $1 - \mathcal{S}(t)$ is consequently the probability that the system has gone fatal up to time t, i.e. the switch has flipped. If no immigration was present, the survival function $\mathcal{S}$ would eventually decay to nil. In the presence of immigration, in contrast, it will eventually attain a constant value. The turnover from the initial to the final state can thereby exhibit a distinct dip, depending on the rate of immigration, i.e. on φ, and the initial number m of particles. This effect is illustrated in Fig. 3. Consequently, in the presence of such a dip the flux

$$\jmath(t) = -\frac{d}{dt}\mathcal{S}(t) \tag{13}$$

will be negative on a certain interval. This causes the associated time constant

$$\int_0^{\infty} t\jmath(t)dt \gtrless 0\,,$$

i.e. it is not a good measure for the underlying process.

A (rather crude) estimate of the characteristic switching time of this process can be obtained from the current $\jmath$. Thus, a lower bound corresponds to the characteristic time of the portion of $\jmath$ before crossing the abscissa: $\underline{\mathfrak{T}} \equiv \int_0^{\tau_0} t\jmath(t)dt$, where $\jmath(\tau_0) = 0$.[15] The upper bound can be obtained from the absolute value of

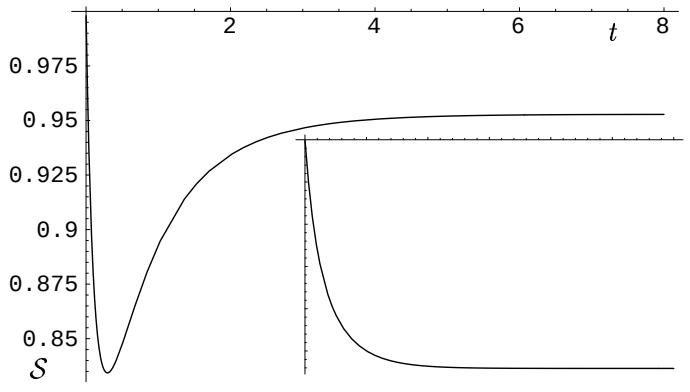

Fig. 3. Survival probability $\mathcal{S}(t)$ for the parameters $m = 2$, $n_{\rm crit} = 2$, and $\varphi = 5$. Inset: monotonic decay for $\varphi = 2$.

the current: $\bar{\mathfrak{T}} \equiv \int_0^\infty t|\jmath(t)|dt$. The most probable switching time corresponds to the minimum in $\jmath$:

$$\mathfrak{T}_{\rm opt} \therefore \frac{d}{dt}\jmath(\mathfrak{T}_{\rm opt}) = 0 \tag{14}$$

and may, for certain ranges of φ be a better estimate for the characteristic switching time of the systems.

3.1. *Co-operativity effects*

Consider now a simple model for a co-operative switch. In such a case, the presence of one representative of the species which has a considerably slower survival (unbinding) rate $k_I \ll k_d$ prevents the switch from flipping, even though the population might temporarily fall below the critical threshold $n_{\rm crit}$. This additional ingredient at a given time being present with probability $1 - P(\emptyset)$, where $P(\emptyset) = k_I/k_d$, as we measure time in units of k_d, the co-operative survival probability yields in the form

$$\mathcal{S}_{\text{co-op}}(t) \equiv 1 - P(\emptyset)(1 - \mathcal{S}(t))\,. \tag{15}$$

By this, we imply that if there are $n \geq n_{\rm crit}$ members present, they will replace the once dissociated I-member in a shorter time scale than the switch can run fatal. Modifications of this law according to the underlying mechanism are, of course, possible.

The characteristic time of this co-operative process is much longer than for the associated process without co-operativity. This is obvious from the prefactor $P(\emptyset)$ in the second term of $\mathcal{S}_{\text{co-op}}(t)$, which will translate into the corresponding expression for $\jmath_{\text{co-op}}(t)$. Similar co-operative effects suppress "accidental" switching in real genetic switches due to fluctuations very efficiently such that the error rate of such switches ranges between $10^{-5} \cdots 10^{-9}$.[1–4,13,14]

3.2. *External triggering of the switch*

So far we have considered the effect of fluctuations on switches. In a real system, changes in the external conditions can induce a flipping of the switch. For instance, in the bacteriophage λ-*E. coli* system, exposition to UV light leads to a fast cleavage of the repressor dimers such that they can no longer attach to the DNA operator sites. The system invariably goes fatal. How fast does the system react? Assuming that the cleavage will be almost instantaneous for free dimers, the rate-limiting step is expected to be the dissociation rate of the I-member, and thus the characteristic flipping rate on external triggering is of the order of k_d/k_I. In particular, this quantity is faster than the fluctuation induction through the survival $\mathcal{S}_{\text{co-op}}$.

4. Time Delay and Long-Tailed Memory

The master equation (3) governing the dynamics of the switch is Markovian, hence local in time. We now explore switches which exhibit a time delay or even a long-tailed memory with diverging time scale. In these cases, the master equation (3) is replaced by the generalized (difference-integrodifferential) master equation[16,17]

$$\frac{\partial}{\partial t}P(n,t) = \int_0^t \mathcal{L}_\varphi P(n,t')\Pi(t-t')dt' \,,$$

$$\mathcal{L}_\varphi P(n,t') \equiv \varphi P(n-1,t') + (n+1)P(n+1,t') - (\varphi+n)P(n,t') \,, \qquad (16)$$

where, in general, the kernel $\Pi(t)$ connects the now-state $P(n,t)$ with its history in the interval $[0,t)$ since system preparation at $t=0$. If Π falls off fast enough on some time scale τ, the system will behave like the standard time-local system (3) for times $t \gg \tau$. Conversely, if it decays slowly, the prehistory of the process is no longer separated from the now-state through a characteristic time scale, and the memory effects become relevant. In such cases, not only the time evolution of the system is affected, but also the probability density function $P(n,t)$ at some given time changes its shape.[18]

Equation (16) can be rewritten in the alternative form[17]

$$\frac{\partial}{\partial t}P(n,t) = \frac{\partial}{\partial t}\int_0^t \mathcal{L}_\varphi P(n,t')\tilde{\Pi}(t-t') \,, \qquad (17)$$

where, in Laplace space

$$\tilde{\Pi}(u) \equiv \int_0^\infty e^{-ut}\tilde{\Pi}(t)dt \,, \qquad \tilde{\Pi}(u) = \Pi(u)/u \,.$$

If the kernel $\tilde{\Pi}$ is of the inverse power-law form

$$\tilde{\Pi}(t) = \frac{(t/\tau)^{\gamma-1}}{\Gamma(\gamma)} \,, \qquad 0<\gamma<1 \,, \qquad (18)$$

the generalized master equation (16) can be rewritten as the fractional equation

$$\frac{\partial}{\partial t}P(n,t) = {}_0D_t^{1-\gamma}\mathcal{L}_\varphi P(n,t) \,. \qquad (19)$$

If we denote by $P_\gamma(n,t)$ the probability density function for $0<\gamma<1$ and by $P_1(n,t)$ its Markovian counterpart (i.e. for $\gamma=1$), then both are related through the generalized Laplace transformation[18]

$$P_\gamma(n,t)=\int_0^\infty E_\gamma(s,t)P_1(n,s)ds\,, \tag{20}$$

where the kernel E_γ can be expressed through the modified one-sided Lévy stable law:

$$E_\gamma(s,t)=\frac{t}{\alpha s}\mathbf{L}_\gamma^+\left(\frac{t}{s^{1/\alpha}}\right)=\frac{1}{s}\sum_{k=0}^\infty\frac{(-1)^k(s/t^\gamma)^{1+k}}{\Gamma(1-\gamma-\gamma k)k!}\,. \tag{21}$$

From the series expansion, analytic representations for special γ can be obtained; e.g. for $\gamma=1/2$, one recovers

$$E_{1/2}(s,t)=(\pi t)^{-1/2}e^{-s^2/(4t)}\,. \tag{22}$$

The probability density function P is plotted for two different times in Fig. 4. Initially, the memory-affected density function $P_{1/2}$ is broader and less peaked than its Markovian counterpart. For longer time, the tails are already approaching each

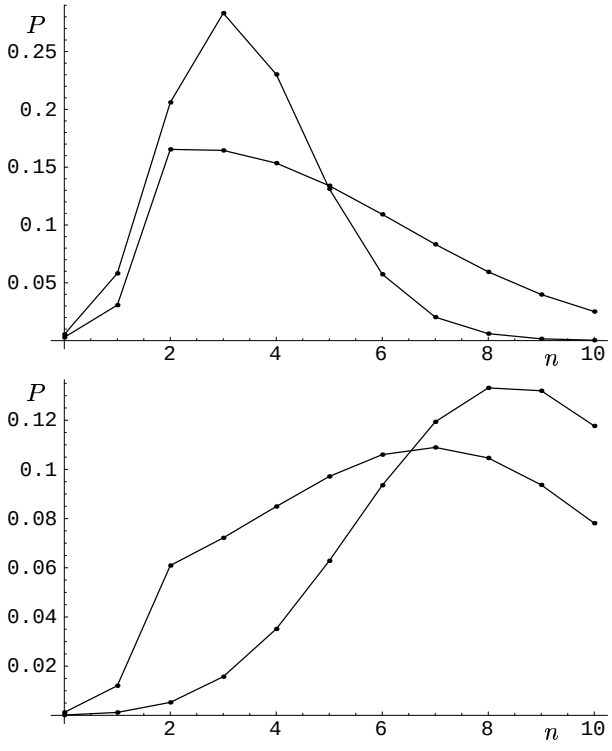

Fig. 4. Probability density functions $P_{1/2}(n,t)$ and $P_1(n,t)$ at times 0.2 (top, P_1 corresponds to the curve with the distinct peak) and 2 (bottom, P_1 has the higher maximum). The plot parameters are $m=2$, and $\varphi=10$.

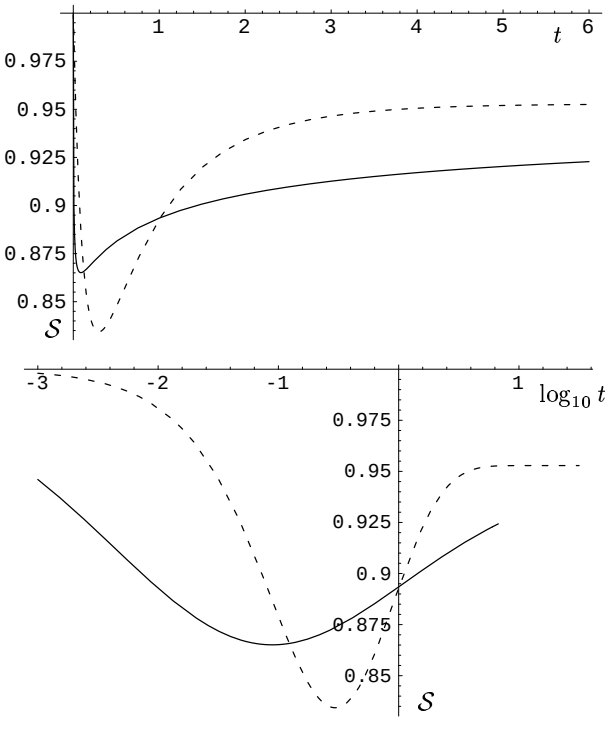

Fig. 5. Survival probability $\mathcal{S}(t)$ for the cases $\gamma = 1/2$ (full lines) and 1 (dashed). Top: linear axes, bottom: logarithmic abscissa. The parameters correspond to the ones in Fig. 4, i.e. $m = 2$ and $\varphi = 10$.

other, whereas for small n the persistence of the initial condition causes the distinct bend. Bends and cusps are typical for long-tailed memory effects.[18] In the plotted example, the broadening of the system due to memory effects lowers the risk to be in a low n situation. As the calculation of the survival function $\mathcal{S}$ is based on the method of images, which does not involve an operation in t, the same transformation can be employed to study the change in behaviour of $\mathcal{S}$. This is depicted in Fig. 5. Again, the broadening of the dip for shorter times and the slow approach to the stationary state in comparison to the Markovian case $\gamma = 1$ is apparent. Here, the shift in the associated probability density function $P_{1/2}$ towards higher n observed in Fig. 4 feeds into the less pronounced drop of $\mathcal{S}$ in the dip region. In exchange, the approach to the stationary behaviour is slower.

Long-tailed memory effects may be more or less pronounced, depending on the actual system parameters. They may help to stabilize the system, especially, for the case without co-operativity when the flipping time may be closer to the dip in the survival probability. Then, the increase in the survival probability will be helpful. Conversely, in the co-operative case the broadening of the survival probability, i.e. the lowering of $\mathcal{S}$ for longer times is of disadvantage. In general, by testing different conditions, it can be observed that the introduction of memory effects may easily reduce the risk of running fatal by a factor of two or more, in the dip range.

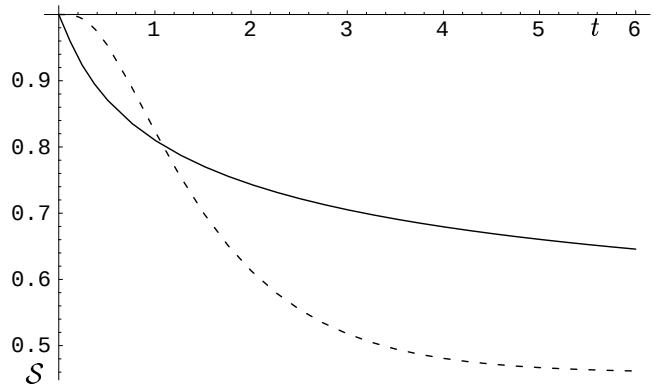

Fig. 6. Survival probability $\mathcal{S}(t)$ for the cases $\gamma = 1/2$ (full lines) and 1 (dashed), for $m = 5$ and $\varphi = 2$: for a monotonic P_1, the trans-Markovian $P_{1/2}$ is almost always lagging behind, improving the survival probability considerably.

If the system has a simple time delay τ, which can, for instance, be modelled by a kernel $\Pi(t, t') = e^{-(t-t')/\tau}$, no simple mapping from the Markovian problem as in the above case of long-tailed memory kernels is possible. One way is to retreat to numerical evaluation of the related generalized master equation. Qualitatively, a memory with existing characteristic time scale can combine the reduction of the dip depth with a fast approach to the stationary state, a situation of choice.

Thus, memory effects tend to smooth out the sharp dips which exist if a comparably small initial number m of members of the population is combined with a large production rate φ. In the case of monotonic decay in the Markovian limit, the introduction of memory will slow down the approach to the stationary state, and thus improve the survival probability for almost all t, as demonstrated in Fig. 6.

In general, these observations suggest that some form of a *trans-Markovian behaviour may be profitable* for a critical switch system; i.e. it enhances the stability of the switch which prefers to stay in the "good" state, and the switch does not flip. This is in qualitative agreement with the finding in Ref. 19 in which a time delay in the cellular signalling chain makes the system more accurate. It should be noted that for a system which is injected in an already existing environment (such as the DNA of bacteriophage λ), a small number m of initial members of the population, and a fairly small enhancement factor φ are appropriate choices for the modelling. Even if φ is relatively large for a given system, a small value of the initial number m of particles still requires the (generalized) discrete-differential (discrete-integrodifferential) master equation approach to describe the fluctuation behaviour on a shorter time scale until continuum behaviour is reached.

5. Conclusions

Real-life biological switches are much more complicated than the idealised switches considered herein. Thus, even the λ-switch combines several degrees of

co-operativity:

(i) Repressor occurs in dimers, and each dimer binds co-operatively to the DNA.
(ii) One repressor dimer facilitates the binding of the second repressor.
(iii) The entire chemistry of transcription, and the positive/negative feedback to the *E. coli*-bacteriophage cycle is highly co-operative.[3]

The entire biochemical cascading of processes underlying the λ switch, still one of the simplest regulatory systems known, is actually extremely involved.[20] Nevertheless, already the ideal switch grasps some of the essential systems characteristics of biological switches. It has the outstanding advantage that it can be treated analytically. In particular, the stability analysis to parameter variations can be investigated in a low-dimensional parameter hyperspace.

The ideal switch considered above was based on the ID-process. In the Markovian case, we gave explicit results for the probability density function, the variance as a measure of fluctuations, as well as calculated the survival probability in the critical threshold model. A particular result is the distinction between systems with a pronounced dip during their transient behaviour and those which decay monotonically, depending on the combination of initial number m and the effective growth rate φ. For the case of a non-vanishing immigration rate k_i, the characteristic switching rate cannot in general be obtained by determining the first moment of the probability current $\jmath$, as it can become negative, or a negative portion of the $\jmath$-function can distort the meaning of the result. A possible way is to consider the most probable switching time $\mathfrak{T}_{\text{opt}}$ if a dip is present, or to interpolate between lower and upper bounds, $\underline{\mathfrak{T}}$ and $\overline{\mathfrak{T}}$.

If trans-Markovian elements are introduced through the generalized master equation with both kinds of memory, with and without characteristic inherent time scale, dips smooth out and for long-tailed memory kernels the approach to the stationary state is slowed down. Whereas the former observation is always good for the system (in the sense that it enhances the probability to stay in the "good" state), the second is disadvantageous if a dip is present (as then it approaches the stationary value from below) and advantageous if no dip occurs. In the case of external induction, memory effects naturally lead to a retarded response. For these reasons, a memory with some intermediate, non-diverging characteristic time scale may be ideal for stabilising the switch. The advantage of response-delay is consistent with the findings reported in Ref. 19. We hope that the present study will instigate some more detailed investigation of this problem.

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References

1. B. Alberts, K. Roberts, D. Bray, J. Lewis, M. Raff and J. D. Watson, The molecular biology of the cell, Garland, New York, 1994; S. R. Bolsover, J. S. Hyams, S. Jones, E. A. Shephard, H. A. White, *From Genes to Cells* (Wiley, New York, 1997).
2. M. Ptashne and A. Gann, *Genes and Signals* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 2002).
3. M. Ptashne, *A Genetic Switch: Phage λ and Higher Organisms* (Cell Press and Blackwell Scientific Publication, Cambridge, Massachusetts, 1992).
4. R. Metzler, *Phys. Rev. Lett.* **87**, 068103 (2001).
5. J.-M. Lehn, *Supramolecular Chemistry* (VCH, Weinheim, 1995); J.-P. Sauvage and C. Dietrich-Buchecker (editors), Molecular Catenanes, Rotaxanes, and Knots: A Journey Through the World of Molecular Topology (Wiley-VCH, Weinheim, 1999).
6. R. Metzler, *Phys. Rev.* **E63**, 012103 (2001); and references therein.
7. A. Hanke and R. Metzler, *Chem. Phys. Lett.* **359**, 22 (2002).
8. R. Metzler and P. G. Wolynes, *Chem. Phys.* **284**, 469 (2002).
9. L. D. Landau and E. M. Lifshitz, *Statistical Physics* (Pergamon Press, London, 1958); J. E. Leffler and E. Grunwald, *Rates and Equilibria of Organic Reactions* (John Wiley, New York, 1963); J. P. Keener and J. Sneyd, Mathematical physiology (Springer-Verlag, New York, 1998).
10. N. G. van Kampen, Stochastic Processes in Physics and Chemistry, North-Holland, Amsterdam, 1981.
11. M. Lax, *Rev. Mod. Phys.* **38**, 359 (1966); *ibid.* **38**, 541 (1966).
12. D. R. Cox and H. D. Miller, *The Theory of Stochastic Processes* (Methuen, London, 1965); N. S. Goel and N. Richter-Dyn, *Stochastic Models in Biology* (Academic Press, New York, 1974); N. T. J. Bailey, *The Elements of Stochastic Processes with Applications to the Natural Sciences* (Wiley, New York, 1964); S. Karlin and J. L. McGregor, *Trans. Amer. Math. Soc.* **86**, 366 (1957); J. W. Haus and K. W. Kehr, *Phys. Rep.* **150**, 263 (1987).
13. E. Aurell and K. Sneppen, *Phys. Rev. Lett.* **88**, 048101 (2002); E. Aurell, S. Brown, J. Johanson and K. Sneppen, *Phys. Rev.* **E65**, 051914 (2002) [cond-mat/0010286].
14. W. Bialek, in *Advances in Neural Information Processing Systems* 13, edited by T. K. Leen (MIT Press, Cambridge, Massachusetts, 2001); cond-mat/0005235.
15. The zero can be found with the corresponding find minimum function in symbolic mathematics programs.
16. V. M. Kenkre, E. W. Montroll and M. F. Shlesinger, *J. Stat. Phys.* **9**, 45 (1973); D. Bedeaux, K. Lakatos-Lindenberg and K. E. Shuler, *J. Math. Phys.* **12**, 2116 (1971); *Stochastic Processes in Chemical Physics: The Master Equation*, edited by I. Oppenheim, K. E. Shuler and G. H. Weiss (MIT Press, Cambridge, Massachusetts, 1977).
17. R. Metzler, *Euro. Phys. J.* **B19**, 249 (2001).
18. R. Metzler and J. Klafter, *Phys. Rep.* **339**, 1 (2000).
19. G. Tiana, M. H. Jensen and K. Sneppen, cond-mat/0207236.
20. A. Arkin, J. Ross and H. H. McAdams, *Genetics* **149**, 1633 (1998); H. H. McAdams and A. Arkin, *Ann. Rev. Biophys. Biomol.* **27**, 199 (1998).