

Delayed decision-making in bistable models

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Abstract—Switching between two modes of operation is a common property of biological systems. In continuous-time differential equation models, this is often realised by bistability, i.e. the existence of two asymptotically stable steady-states. Several biological models are shown to exhibit delayed switching, with a pronounced transient phase, in particular for near-threshold perturbations. This study shows that this delay in switching from one mode to the other in response to a transient input is reflected in local properties of an unstable saddle point, which has a one dimensional unstable manifold with a significantly slower eigenvalue than the stable ones. Thus, the trajectories first approximatively converge to the saddle point, then linger along the saddle’s unstable manifold before quickly approaching one of the stable equilibria.

I. INTRODUCTION

Biological systems are complex networks involving many reactions, feedback loops and connections. One recurrent motif in continuous-time models is the implementation of binary decision by means of bistable switches. Examples of such models include cell cycle progression [1], [2], [3], cell death signalling [4], developmental processes [5], [6], signal responses with memory such as in EGF signalling [7], [8], infectious diseases such as prion propagation [9] or lambda phage infection [10], and a synthetic toggle switch [11].

In several of these bistable systems, the switch is triggered by a sufficiently large input signal. Often, this is accompanied by a delayed decision making mechanism, in particular for inputs near the threshold. This article uncovers the importance of the usually neglected saddle point, and the dynamics in its proximity in three bistable biological models. Analysing the system responses shows that this delayed switching serves as a robust mechanism to allow for reverting the decision by small perturbations.

The paper is structured as follows. Section II describes how bistable systems act as switches in continuous models and introduces the concept of delayed decision making. The latter is linked to properties of the saddle point in Section III. The here proposed analysis is then applied to two published, higher dimensional models of programmed cell death (Section IV). The paper closes with a discussion and conclusions.

II. BISTABLE SYSTEMS AND DELAYED DECISION MAKING

Bistable systems have the ability of modelling switch-like decisions in continuous-time systems [12]. These can be reversible or not, depending on the precise setup. In most cases,

the bistable models contain not only two asymptotically stable equilibrium points, but also a saddle point as depicted in Figure 1. In a two-dimensional model, the stable manifold of the saddle corresponds to the separatrix of the two stable equilibria while the saddle’s unstable manifold connects all three equilibria. This phase portrait is illustrated in Figure 1. This picture actually extends to many higher dimensional models of dimension n with an $n - 1$ dimensional stable manifold and a 1 dimensional unstable manifold.

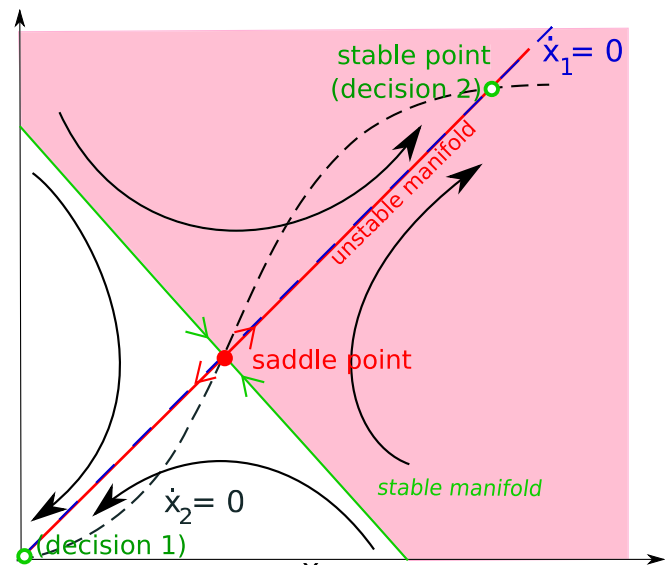


Fig. 1. Phase plane of a typical bistable system in two dimensions. The stable manifold of the saddle point divides the phase plane in the two basins of attraction of the stable equilibria. A perturbation pushing the trajectory across the separatrix induces a switch in the final decision.

A. Bistable systems: decision making on transient signal

Bistable systems are particularly useful for transforming short-duration input signals in permanent decisions. When transient inputs are applied, the equilibrium points remain unchanged. Starting in one of the steady-states, eg. the unexcited one, the input can trigger the switch if the input signal is sufficiently strong. For a signal of particular shape, it is possible to define an *input transition threshold* such that any larger input activates the switch while any smaller one does not.

An intriguing property of several bistable system models is that the response near the threshold is significantly delayed, as illustrated in Figure 2. This figure depicts the responses

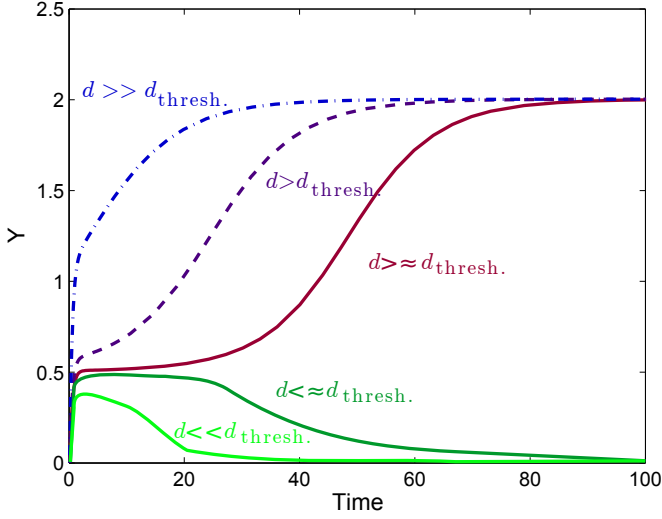


Fig. 2. Output trajectories for increasing impulse inputs. Near the threshold, the final decision ($y = 0$ or $y = 2$) is significantly delayed.

of a model of genetic control proposed by [13] where a protein x_1 enhances the production of the mRNA x_2 which is translated into the protein itself. The model is modified here to include an input u and an output y :

$$\dot{x}_1 = -ax_1 + x_2 \quad (1a)$$

$$\dot{x}_2 = \frac{x_1^2}{1+x_1^2} - bx_2 + u \quad (1b)$$

$$y = x_1, \quad (1c)$$

with the two states $x_1, x_2 \in \mathbb{R}_{\geq 0}$, and the parameters $a, b > 0$ describing the rate of degradation of x_1 and x_2 . Figure 3 depicts the corresponding phase plane.

The model (1) is bistable as it has two stable equilibrium points (green dots) and one saddle point (red dot) located at the intersection of the nullclines (blue and gray dashed curves). The stable state corresponding to low values of x_1 and x_2 can be named unexcited state while the other can be named excited state. The saddle point has one attractive direction (stable manifold, in green) and one repulsive direction (unstable manifold direction, in red). The stable manifold of the saddle point divides the phase plan into two regions corresponding to basins of attraction of the two stable equilibrium points.

We study the system responses with the unexcited steady-state as initial condition and an impulsive input u with height d , ie.

$$u(t) = d\delta(t) \quad (2)$$

where $\delta(t)$ is the Dirac impulse. This shows that there is a threshold \bar{d} such that for all $d < \bar{d}$ the trajectory returns to the initial equilibrium point, while for all $d > \bar{d}$ the trajectories tend to the excited equilibrium. Furthermore, the convergence time to the excited steady state depends on the input amplitude: the larger the input, the faster the response.

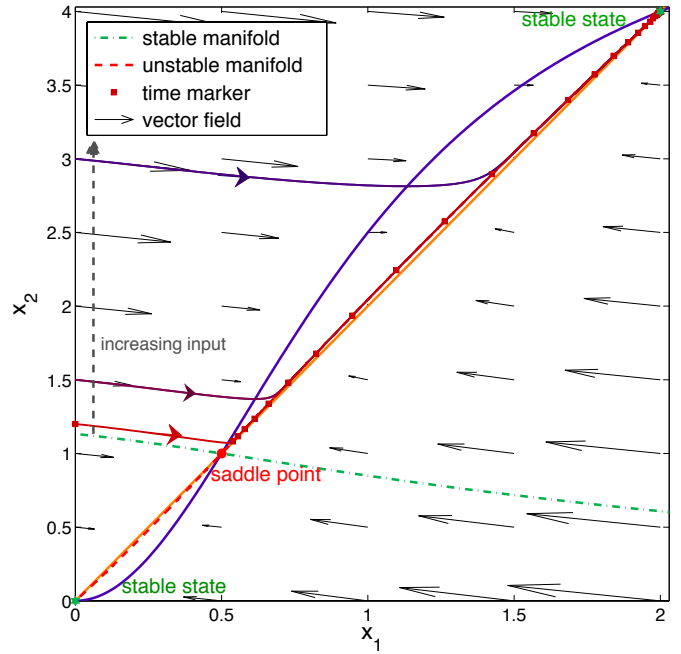


Fig. 3. Phase plane for the model of Griffith (1). The nullclines $dx_1/dt = 0$ (orange line) and $dx_2/dt = 0$ (blue line) intersect at the equilibrium points. The stable and unstable manifold of the saddle point are shown by green and red dashed lines, respectively. Equidistant time markers (dark red squares) highlight the temporal evolution along the unstable manifold.

TABLE I
SADDLE POINT PROPERTIES

	Griffith (1)	Eissing [4]	Schliemann [14]
λ_+	0.1	$1.0 \cdot 10^{-4}$	$2.6 \cdot 10^{-5}$
λ_-	-2.3	$-1.1 \cdot 10^{-3}$	$-5.6 \cdot 10^{-5}$
$r = \lambda_-/\lambda_+ $	23.0	11.0	2.2
stable dimensions	1	7	36

Unstable (λ_+) and slowest stable (λ_-) eigenvalues of the saddle point in the three studied models, as well as ratio r of the magnitude of these two eigenvalues and the dimension of the stable manifolds.

B. Delayed decision making

Simulations of the model (1), shown in the phase plane in Figure 3, reveals that the trajectories quickly approach the unstable manifold of the saddle point and linger along it towards one of the stable equilibria. This lingering is particularly pronounced for input signals that are close to the input transition threshold. Figure 2 shows the response of (1) to impulses above to marginally above the input transition threshold. The closer the magnitude is to this threshold, the longer the output remains on an intermediate value. A closer look at the corresponding phase plane (Figure 3) reveals that during this intermediate phase, the state evolves close to the unstable manifold of the saddle point, which is furthermore the slow manifold of both stable steady-states. We call such a switching behaviour with long transients close to the input threshold *delayed decision making*.

An important consequence of a delayed decision making is illustrated in Figure 4. As the system remains close to the saddle point and thus to the separatrix during the intermediate phase, a small input perturbation allows for

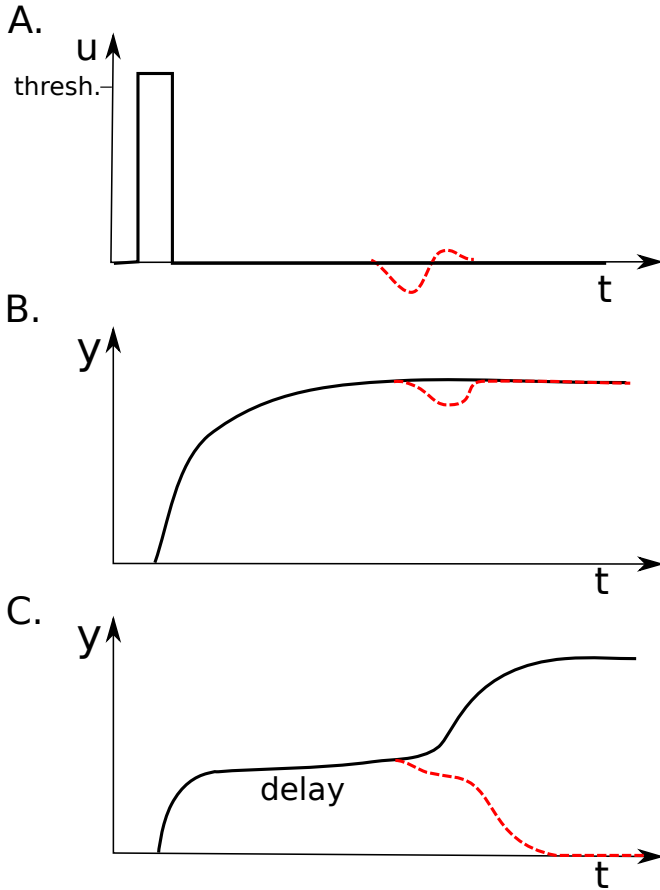


Fig. 4. Output trajectory for a bistable systems with or without time scale separation, starting at the unexcited steady-state. (A) The input signal is chosen slightly larger than the threshold for activating the switch (solid line). A small input perturbation is shown in red. (B) For a bistable system without time separation, the system quickly switches and the output is soon close to the excited state. The input perturbation has little effect. (C) For a bistable system with time scale separation, the output remains at an intermediate value as the system evolve close to the saddle point for a long period of time. During this interval, a small perturbation can push the trajectory back into the domain of attraction of the unexcited steady-state, thus preventing the switching to occur.

reverting the switching decision. This is shown by the red dashed signals in Figure 4. Thus, such delayed decision making system is very sensitive to reverting perturbations during this intermediate phase. Such a property could have biological significance in a signalling mechanism.

III. LOCAL SIGNATURE OF DELAYED DECISION MAKING

The just described decision making is caused by the temporary attractivity of the saddle point, enforced by a time scale separation between the (slowest) stable eigenvalue (λ_-) of the Jacobian and the unstable one (λ_+). The ratio r

$$r = \left| \frac{\lambda_-}{\lambda_+} \right| \quad (3)$$

is thus a simple measure of the stiffness of the saddle point and quantifies locally this time scale separation between its stable and unstable manifolds. This ratio r is a local signature

of delayed decision. A high ratio is an indicator that the attractive direction is much faster than the repulsive one.

Delayed decisions are induced by time scale separation between the attractive and the repulsive direction of the saddle point. This causes trajectories passing close to the separatrix to rapidly converge to the neighborhood of the saddle point, along the saddle point's stable manifold. They then slowly escape in the direction of the unstable manifold. The speed can be inferred from the time markers (red squares in Figure 3). Thus, the pronounced time scale separation of the saddle point is visible in trajectories that have been induced by inputs close to input transition threshold and furthermore result in input strength dependent transition delays. Moreover, the duration of the delayed decision making is inversely correlated to the closest distance to the saddle point.

IV. DELAYED DECISION IN HIGHER DIMENSIONAL MODELS

Delayed decision making is also observed in higher dimensional models. A typical example is the signalling pathway of apoptosis, the predominant form of programmed cell death used by multicellular organisms to remove superfluous, damaged or potentially harmful cells [15]. A variety of models of apoptosis have been proposed, see [16] for an overview of models of apoptotic signalling. Several of them include a positive feedback loop of caspase interaction, which leads for suitable parameters to a bistable system. One of these is the model by Eissing et al. [4] that describes the interaction of two caspases (Caspase 3 and 8) and two inhibitors (XIAP and CARP), see Figure 5. Initiator caspases activate effectors caspases which trigger the cellular processes leading to death. The survival state corresponds to a state with low concentration level of effector caspases while death corresponds to high level. Input signal correspond to impulsions modelling the effect of a transient pro-apoptotic signal. The system's input has been slightly modified with regard to the original model proposed by Eissing et al. In the present analysis, input signal directly acts on the number of initiator caspases that become activated ($C_8 \rightarrow C_8^*$) rather than a extra inflow of active initiator caspases [17]. The system's output is defined as the concentration level of activated caspase 3 ($C3^*$). There is an input threshold corresponding to 75 molecules of $C3^*$, above which the system switches to death.

The model in [4] is a set of 8 nonlinear ordinary differential equations. The model is bistable and the two stable steady-states correspond to survival and death, respectively. For inputs close to the input threshold, the trajectories approach the saddle point [18]. Figure 6 shows output trajectories for increasing impulse input signals above input threshold. The system clearly presents a delayed decision making that depends on the input strength. Even though this model has been analysed in many publications, none has yet emphasised the role of the saddle point in time delays between stimulus application and cell death.

Table II lists the eigenvalues at the saddle point. The system has only one positive eigenvalue, which is in addition

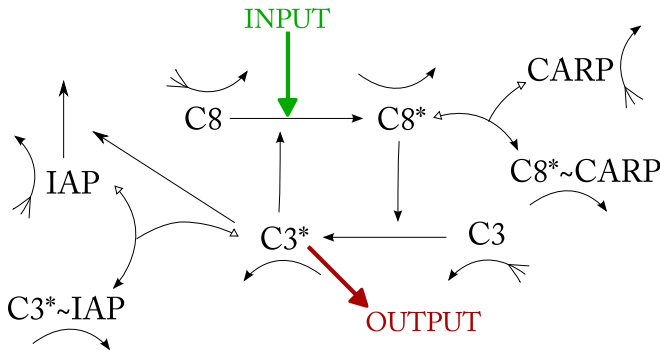


Fig. 5. Eissing et al. model. Input act on the number of molecules of initiator caspase 8 (C8) that become activated (C8*). The output corresponds to the concentration of activated effector caspase 3 (C3*).

TABLE II
EIGENVALUES OF THE JACOBIAN AT THE SADDLE POINT OF THE
EISSING MODEL [4].

-21.2165
-18.7366
-0.0270
-0.0117
-0.0039
-0.0039
-0.0011
0.0001

the eigenvalue with the smallest absolute value of all the eigenvalues. Table I shows that the two slowest eigenvalues are an order of magnitude apart. The time scale separation explains the fast attraction towards the saddle point and the lingering along its slow, unstable manifold towards one of the stable steady-states. This time scale separation can also be observed in Figure 7. The responses to inputs close to the transition threshold converge quickly to the neighbourhood of the saddle point, before escaping slowly along its unstable manifold, which corresponds to the slow direction. As the saddle point is close to the survival steady-state, the cell behaviour during the decision-making phase is very similar to survival.

The analysis was also applied to a significantly larger model of 37 states. This model describes the pro- and anti-apoptotic signalling [14] pathways induced by the stimulation by the cytokine TNF of NF- κ B, an important transcription factor for anti-apoptotic proteins. At the same time, TNF internalises and then activates the initiator caspase Caspase 8, which is part of a positive feedback loop of mutual activation of Caspase 8, Caspase 3 and Caspase 6. This system is also a bistable system with a saddle point having only one positive eigenvalue which furthermore is the smallest in magnitude, see Figure 9. The ratio is less pronounced here, approximatively a factor two. This is still enough to generate a delayed decision making for inputs close to the input threshold.

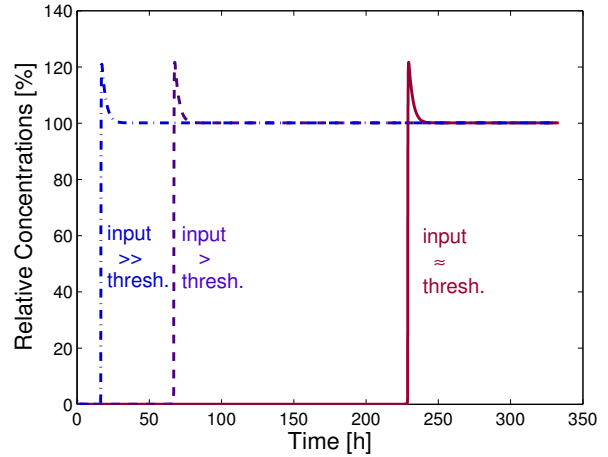


Fig. 6. Output trajectories of Eissing model [4] for impulse inputs slightly above (red), above (magenta) and significantly above (blue) the decision making threshold.

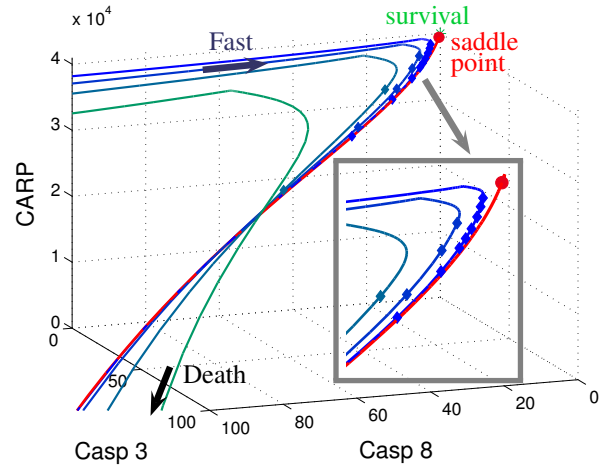


Fig. 7. Trajectories of the Eissing model for increasing impulse inputs: Blue curves correspond to trajectories for inputs close to the transition threshold while green curves depict trajectories for larger inputs. The inset is a zoom of the neighbourhood of the saddle point.

Figure 8 shows the delayed decision making for different input intensities. In particular for inputs slightly above the threshold, the delay is quite significant (about one day). Visualising the trajectories in the state space illustrates the importance of the saddle point and of its unstable manifold. Inputs close to the transition threshold result in trajectories that first converge to the proximity of the saddle point before diverging along the unstable manifold. As the stiffness of the saddle is smaller than in the other two previously studied models, the convergence is less pronounced for inputs not very close to the threshold.

V. DISCUSSION

Model comparison is an important problem in systems biology. However, the comparison of different bistable systems of different dimensions is difficult. In many cases,

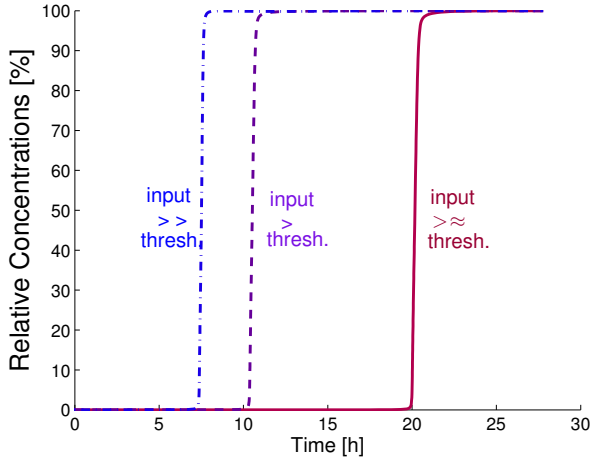


Fig. 8. Output trajectories of Schliemann model [14] for impulse inputs slightly above (red), above (magenta) and significantly above (blue) the decision making threshold.

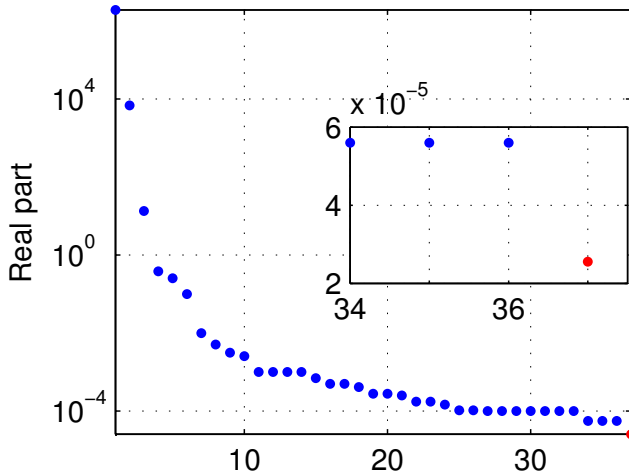


Fig. 9. Eigenvalues of the Jacobian at the saddle point in the Schliemann model [14], stable ones in blue, unstable in red. The inset zooms in on the four slowest eigenvalues.

only the stable equilibrium points are analysed. This study demonstrates that local analysis of an unstable point, the saddle point, may add very useful information to the analysis. In particular, its time-scale separation captures the delayed decision making mechanism, not visible in the two stable equilibria. Two published models of apoptosis show the relevance of the presented approach.

As for the Griffith model, time scale separation between attractive directions and repulsive direction of the saddle point leads to input-strength dependent time delays in higher dimensional models. The analysis of the models [14], [4] show that the mechanism of delays induced by time-scale separation between attractive and repulsive directions of the saddle point, can be observed in higher dimensional models. These models are much more difficult to analyse. This highlights the usefulness of the quantification of delayed

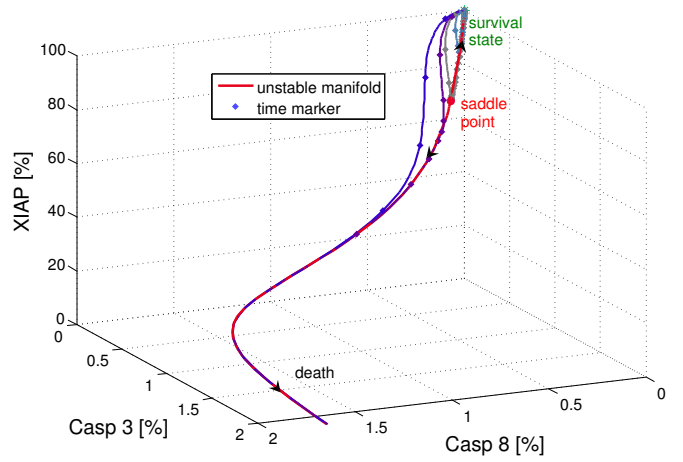


Fig. 10. Trajectories of the Schliemann model [14] for increasing impulse inputs. The light blue curve corresponds to the trajectory for an input below the transition threshold, while the gray one to an input slightly below this threshold. Both converge to the survival state. The magenta one is slightly above and the blue one even more above the threshold. Both converge to the death state. The axes are normalised by the values at the death steady-state for Caspase 8 and Caspase 3 and by the value at the survival steady-state for XIAP.

decision making via the ratio of unstable and slowest stable eigenvalues of the saddle point.

VI. CONCLUSION

This study highlights the importance of the saddle point in delayed decision making in bistable switches. In particular, the ratio of the magnitudes of the unstable and the slowest stable eigenvalue is a simple local measure of stiffness not only locally around this unstable equilibrium, but also for trajectories induced by inputs close to the input transition threshold. The time-scale separation between attractive and repulsive direction of the saddle point creates a robust mechanism for delayed decision making. Its usefulness has been illustrated at the hand of models of apoptotic signalling. The delayed decision making phase could be used by anti-apoptotic signals to revert the path to cell death.

Future work will provide a global analysis of the heterocline connecting the three equilibria and also analyse further biological models of delayed switching.

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