

## COMPARISON OF DIFFERENT TYPES OF DELAYS IN A MATHEMATICAL MODEL OF EMT–MET DYNAMICS

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### ABSTRACT

We investigate the role of time delays in a mathematical model describing the dynamics of TGF- $\beta$  in epithelial–mesenchymal transition (EMT) and mesenchymal–epithelial transition (MET) in cancer cells. The model describes the dynamics of free and receptor-bound TGF- $\beta$ , with the latter representing the biologically active form of the protein. Starting from a kinetic model of TGF- $\beta$  dynamics, we introduce a time delay to account for the fact that the biological effects associated with TGF- $\beta$  binding may depend not only on the current state of the system, but also on its past states.

We focus on the comparison of different representations of delayed processes. In particular, we consider the classical model without delay and a model with a discrete delay, in which the influence of the past is represented by a single fixed time lag. Such a formulation leads to a system of delay differential equations in which the past value of free TGF- $\beta$  directly affects the current production of the bound form. The resulting model is analysed with respect to the existence, uniqueness, non-negativity and boundedness of solutions, as well as the stability of its equilibrium states.

For the model with discrete delay, we show that the set of non-negative initial functions is positively invariant and that solutions exist globally in time. We identify the conditions under which the trivial equilibrium and the positive equilibrium exist and determine their stability properties. In particular, under appropriate parameter conditions, the stability of the equilibrium states is independent of the magnitude of the discrete delay. The analysis is supported by characteristic equations and Lyapunov functionals formulated in the appropriate phase space of continuous history functions.

The influence of the delay representation on the model dynamics is further investigated numerically. Solutions of the delayed and non-delayed models are compared for biologically motivated parameter values and consistent history functions. The simulations demonstrate that the introduction of a discrete delay may generate transient oscillations while preserving the asymptotic stability of the positive equilibrium. At the same time, the effect of the delay is particularly visible in the variable directly affected by the delayed term, highlighting the importance of an appropriate representation of biological memory.

As a further step, we consider the extension of the model towards distributed delays, in which the past states of the system influence the present dynamics over a whole interval of time rather than at a single prescribed time point. This formulation allows different distributions of biological response times to be incorporated through a delay kernel and provides a more flexible description

of intracellular signalling processes. We compare the mathematical properties and dynamical behaviour associated with discrete and distributed delays, with particular emphasis on their influence on stability, transient dynamics and the biological interpretation of the model.

The comparison highlights the limitations of representing a biologically heterogeneous response time by a single discrete delay and motivates the use of distributed-delay models as a potentially more realistic framework for describing delayed TGF- $\beta$  signalling during EMT/MET. The results provide a mathematical basis for selecting an appropriate delay formulation in models of cancer-cell plasticity and for further investigation of how different types of biological memory affect the long-term dynamics of the system.

## REFERENCES

- [1] T. Celià-Terrassa et al.: *Hysteresis control of epithelial-mesenchymal transition dynamics conveys a distinct program with enhanced metastatic ability*, Nat. Commun. **9** (2018).