Dynamics of a transport mediating switch

Tomáš Gedeon [*1], **Erik Boczko** [2], and **Konstantin Mischaikow** [3]

[1] Department of Mathematical Science, Montana State University, Bozeman, MT 59715, USA.

[2] Department of Biomedical Informatics, Vanderbilt University, Nashville, TN 37232, USA.

[3] Department of Mathematics and BioMaPS Institute, Hill Center-Busch Campus, Rutgers, The State University of New Jersey, Piscataway, NJ 08854-8019, USA.

We show that dynamics of a general toggle switch that mediates transport between cellular compartments, converges to a unique periodic orbit in two limiting cases. These results can be perturbed for a restricted, but biologically ubiquitous model. This robustness may be the reason why only the restricted switch appears to be operating in Nature.

1 Introduction

We study the dynamics of a model toggle switch abstracted from the genetic interactions operative in a fungal stress response circuit. The switch transduces an external signal by mediating the transport between compartments of two interacting gene products. The ubiquity and modularity of this cellular control mechanism warrants a detailed study of the dynamics entailed by various modelling assumptions. We consider 1. a general gate model in which both of the associating proteins are freely transportable between compartments and 2., a model where only one of the two proteins undergoes transport. The second model, while seemingly more restrictive, is actually implemented in all biological examples we found in the literature [1].

Under the strong assumption that the disassociation of the interacting proteins is unidirectional we show that the qualitative dynamics of the two models are similar; that is they both converge to unique periodic orbits. We show that the same result holds for the model **2.** when one weakens the assumption of unidirectional binding or disassociation. We speculate that this is not true for the more general model. This difference in dynamics may have important biological implications.

2 The model

We present a mathematical model for the general two compartment gating switch (model **1.** above) and then provide a biological interpretation for each of the terms in the context of a eukaryotic cell. Consider

$$
\begin{aligned}
\dot{x} &= K_{imp}^0 \left(\int_{-\tau}^0 b_\xi(s)\xi(t+s)\,ds \right) - K_{exp}^0(x) - \alpha x \\
\dot{X} &= h_0(t) - \beta X \\
\dot{\xi} &= T^0(X(t-\delta_1)) - \gamma\xi - k_f g(\xi,\mu) + k_r C + K_{exp}^0 \left(\int_{-\tau}^0 b_x(s)x(t+s)\,ds \right) - K_{imp}^0(\xi) \\
\dot{u} &= K_{imp}^1 \left(\int_{-\tau}^0 b_\mu(s)\mu(t+s)\,ds \right) - K_{exp}^1(u) - \eta u \\
\dot{U} &= h_1(t) - \theta U \\
\dot{\mu} &= T^1(U(t-\delta_2)) - \kappa\mu - k_f g(\xi,\mu) + k_r C + K_{exp}^1 \left(\int_{-\tau}^0 b_u(s)u(t+s)\,ds \right) - K_{imp}^1(\mu) \\
\dot{C} &= k_f g(\xi,\mu) - k_r C
\end{aligned}
\tag{1}
$$

Two proteins lie at the heart of this regulatory switch. In the nucleus, the concentrations of these proteins are x and u. The concentrations of the same proteins in the cytoplasm are denoted by ξ and μ. Finally, these proteins are produced from distinct mRNA whose concentration in the cytoplasm are X and U, respectively. Degradation and the volume growth of the cell decreases the concentrations of the proteins and mRNA. We assume that this happens at constant strictly positive rates α, β, γ, η, θ, and κ.

To model the transportation of protein between compartments we assume that the cytoplasmic protein arriving at the nucleus at time t left the cytoplasmic compartment earlier, that is at some moment in the time interval $[t, t-\tau]$ for a fixed $\tau > 0$. The amount that arrives is specified by the kernel functions $b_\xi(s) \geq 0$ and $b_\mu(s) \geq 0$ with support in $[-\tau, 0]$. This gives rise to the terms $\int_{-\tau}^0 b_\xi(s)\xi(t+s)\,ds$ and $\int_{-\tau}^0 b_\mu(s)\mu(t+s)\,ds$. Similar comments apply to the transport of the proteins from the nucleus

* Corresponding author: e-mail: gedeon@math.montana.edu, Phone: +406 994 5359, Fax: +406 994 1789

to the cytoplasm. While these terms model the amounts transported, the rates of nuclear import and export are concentration dependent [2] and we model them by nuclear import and export rate functions $K_{imp}^*(\cdot)$ and $K_{exp}^*(\cdot)$, $* = 0, 1$. We assume that the proteins are constitutively expressed and that the cell cycle is periodic with period r. Then the rate of production of the mRNA is given by periodic functions $h_0(t)$ and $h_1(t)$, respectively, with period r.

Again, at this level of generality detailed knowledge concerning the translation process is unknown. Thus, we denote by $T^*(\cdot)$, $* = 0, 1$ concentration dependent translation initiation rate functions, and denote by δ_1 and δ_2 delays that take into account the elongation and folding of the nascent protein.

The gating control mechanism is as follows. The two cytoplasmic proteins can combine, according to an association function $g(\xi, \mu)$, to form a complex whose cytoplasmic concentration is given by C. The rate of association of C from its constituents is k_f and rate of dissociation is k_r. We assume that the complex is incapable of entering the nucleus.

These comments provide the biological justification for each of the terms in (1). The precise mathematical assumptions (**H**) are as follows:

1. The right-hand side of system (1) needs to be at least C^1. The transport rate functions $K_*^\#$, $* = exp, imp$ and $\# = 0, 1$, are monotone bounded from above and for $s \geq 0$ satisfy $K_*^\#(s) = 0$ if and only if $s = 0$. Further, the functions T^i, $i = 0, 1$, are positive for $s > 0$ and $\frac{\partial g}{\partial \xi} > 0$ and $\frac{\partial g}{\partial \mu} > 0$ are positive.

2. The kernel functions satisfy $b_z(s) \geq 0$, $b_z([-\tau, -\tau + \epsilon]) > 0$ for small ϵ, and the amount of protein coming out of the transport compartment is not larger than the amount that entered the compartment. In other words,

$$\int_{-\tau}^{T-\tau} K_*^\#(z(t))\, dt \geq \int_0^T K_*^\# \left(\int_{-\tau}^0 b_z(s) z(t+s)\, ds \right) dt$$

for all $T \geq \tau$, $z = x, \xi, u, \mu$, $* = exp, imp$ and $\# = 0, 1$.

If the system (1) represents a general switch (model **1**) the more restrictive switch (model **2**) is represented by (1) with $u \equiv 0$. This describes the situation when one of the proteins cannot enter one of the compartments. The main results are summarized in the following Theorem.

Theorem 2.1 *Consider (1) and assume the hypothesis* (**H**) *are satisfied.*

a. *If $k_f = 0$ and $r \geq 2\tau$, then there is a unique r periodic solution $\Gamma(t, t_0)$ which is a global attractor for any admissible initial condition.*

b. *If $k_r = 0$ and $r \geq 3\tau$ then there is a unique r periodic solution $\Gamma(t, t_0)$ which is a global attractor for any admissible initial condition.*

Consider (1) with $u \equiv 0$ and assume (**H**).

c. *There exists $\epsilon_f > 0$, such that if $0 \leq k_f < \epsilon_f$ and $r \geq 2\tau$, then there exists a unique r periodic solution $\Gamma(t, t_0)$ which is a global attractor for any admissible initial condition.*

d. *There exists $\epsilon_r > 0$, such that if $0 \leq k_r < \epsilon_r$ and $r \geq 3\tau$, then there exists a unique r periodic solution $\Gamma(t, t_0)$ which is a global attractor for any admissible initial condition.*

The phrase "for any admissible initial condition" refers to any initial condition in the appropriate phase space, which, due to delays in the system, time-dependent forcing, and non-negativity constraint on concentrations, are cones in the appropriate Banach spaces [1]. The reader is referred to ([1]) for proof of the Theorem.

References

[1] E. Boczko, T. Gedeon and K. Mischaikow, Dynamics of a simple regulatory switch, *J. Math. Biol.* (2008), Online first:DOI 10.1007/s00285-007-0102-x.

[2] Ribbeck,K.and Gorlich,D. Kinetic analysis of translocation through nuclear pore complexes, *EMBO* **20**, 1320-1330 (2001).