

Identification of Optimality and Robustness in *Dictyostelium* External Signal Receptors ^{*}

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Abstract: Robust optimal performance of ligand and receptor interaction networks in cellular systems is essential in order for organisms to react appropriately to external stimulation. Recent studies have proposed that certain generic structural properties are highly conserved among the many different types of ligand/receptor interaction networks found in nature. In this paper, we show that the ligand/receptor interaction network employed to relay external cAMP signals in aggregating *Dictyostelium discoideum* cells exhibits such generic structural characteristics. We also show that the network parameters for the ligand bound cell receptors which are distributed on the outer shell of *Dictyostelium discoideum* cells are highly optimised, in the sense that the response speed is the fastest possible while ensuring that no overshoot occurs for step changes in external signals. Finally, we show that the response of the network to external signals is extremely robust to variations in the relevant kinetic parameters of the network, the cell volume and the number of receptors present on the surface of the cell.

Keywords: Biocybernetics; Optimality; Robustness.

1. INTRODUCTION

In cellular signal transduction, external signalling molecules, called ligands, are initially bound by receptors which are distributed on the cell surface. The ligand-receptor complex then initiates various signal transduction pathways, such as activation of immune responses, growth factors, etc. Inappropriate activation of signal transduction pathways is considered to be an important factor underlying the development of many diseases. Hence, robust performance of ligand and receptor interaction networks constitutes one of the crucial mechanisms for ensuring the healthy development of living organisms.

In Endres et al. [2007], a kinetic model for how the distribution of chemoreceptor complexes affects the cell response was developed from time series responses to perturbations in ligand concentration. By analysing this model it was identified that the distribution of complex size in the membrane depends on the receptor free energy. Physical details about ligand-receptor interactions are discussed in Bongrand [1999]. In a recent study, Shankaran et al. [2007] proposed a generic structure for ligand-receptor interaction networks and showed that the ability to capture

ligand together with the ability to internalise bound-ligand complexes are the key properties distinguishing the various functional differences in cell kinetics.

The above studies have highlighted the fact that striking structural similarities exist between the various different types of interaction networks found in nature. From the perspective of Control Engineering, it is also tempting to speculate that nature will have evolved the parameters in such structural networks to deliver robust and optimal performance in relaying external signals into the cell [Barkai and Leibler, 1999, Csete and Doyle, 2002, Morohashi et al., 2002, Kurata et al., 2006, Ciliberti et al., 2007]. In this paper we provide a specific example of a cellular system which seems to support both of the above hypotheses.

Dictyostelium discoideum are social amoebae which live in forest soil and have been widely used as model organisms for studying molecular biology [DictyBase]. *Dictyostelium* cells grow independently, but under conditions of starvation they initiate a well-defined program of development [Laub and Loomis, 1998]. In this program, the individual cells aggregate by sensing and moving towards gradients in cAMP (cyclic Adenosine Mono-Phosphate), a process known as chemotaxis, to form complexes of up to 10^5 -cells. Subsequently, the individual cells form a slime mold which eventually becomes a fruiting body which emits spores.

^{*} This work was supported by BBSRC research grant BB/D015340/1.

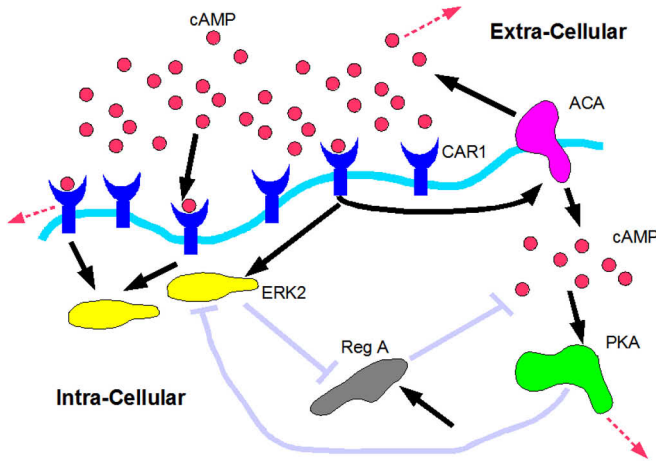


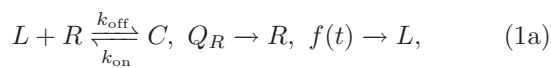
Fig. 1. The model of Laub and Loomis [1998] for the network underlying cAMP oscillations in *Dictyostelium*. The normal arrows and the broken arrows represent activation and self degradation, respectively. The bar arrows represent inhibition.

The early stage of aggregation are initiated by the production of spontaneous oscillations in the concentration of cAMP (and several other molecular species) inside the cell. In Laub and Loomis [1998], Maeda et al. [2004] a model, consisting of a set of nonlinear ordinary differential equations, was developed for analysing the processes underlying these spontaneous oscillations in the early stages of *Dictyostelium* aggregation. Note that the oscillations for each individual cell are not completely autonomous, but are excited by changes in the concentration of external cAMP, which is secreted from each cell and diffused throughout the region where the cells are distributed. Thus, for this system, external cAMP molecules constitute the ligand, while molecules on the surface of the *Dictyostelium* cells called CAR1 (Catabolism of ARginine) constitute the receptors.

In this paper, we show that the above ligand/receptor interaction network exhibits the generic network structure postulated in Shankaran et al. [2007]. We also show that the parameters for this network appear to be highly optimised from a Control Engineering perspective, in the sense that the response to step changes in external signals is the fastest possible while ensuring that no overshoot occurs. Finally, we show that the response of the network to external signals is extremely robust to variations in the relevant kinetic parameters of the network, the cell volume and the number of receptors present on the surface of the cell.

2. A GENERIC STRUCTURE FOR LIGAND/RECEPTOR INTERACTION NETWORKS

Shankaran et al. [2007] proposed a generic structure for cellular ligand/receptor interaction networks of the following form:



where L is the ligand concentration, R is the number of external cell receptor molecules, C is the number of ligand-receptor complex molecules, k_{on} is the forward reaction rate for ligands binding to receptors, k_{off} is the reverse reaction rate for ligands dissociating from receptors, k_t is the rate of internalisation of receptor molecules, k_e is the rate of internalisation of ligand-receptor complexes, Q_R is equal to $R_T \times k_t$. R_T is the steady state number of cell surface receptors when $C = 0$ and $L = 0$, \emptyset is the sinks of either the receptor or the complex, $f(t)$ is some input signal and t is time. The corresponding differential equations are given by

$$\frac{d}{dt} \begin{bmatrix} R \\ C \\ L \end{bmatrix} = \begin{bmatrix} -k_{on}RL + k_{off}C - k_tR + Q_R \\ k_{on}RL - k_{off}C - k_eC \\ (-k_{on}RL + k_{off}C) / (N_{av}V_c) + f(t) \end{bmatrix} \quad (2)$$

where N_{av} is Avogadro's number, 6.023×10^{23} and V_c is the cell volume in liters throughout which the receptors are distributed,

In normalised form, the above equation can be written as

$$\frac{d}{dt^*} \begin{bmatrix} R^* \\ C^* \\ L^* \end{bmatrix} = \begin{bmatrix} -R^*L^* + C^* - \alpha(R^* - 1) \\ R^*L^* - C^* - \beta C^* \\ \gamma(-R^*L^* + C^*) + u \end{bmatrix} \quad (3)$$

where $t^* = k_{off} t$, $R^* = R/R_T$, $C^* = C/R_T$, $L^* = L/K_D$, $u = f(t)/k_{off}/K_D$ and K_D is the receptor dissociation constant, i.e., $K_D = k_{off}/k_{on}$, α is a quantity proportional to the probability of internalisation of unbound receptors, β is a quantity proportional to the probability of internalisation of captured ligand by receptors before dissociation of the ligand from the receptors, and γ represents the level of sensitivity of the receptors to the external signals [Shankaran et al., 2007]. By assuming that the number of receptors is much larger than the number of ligands, i.e. $dR/dt \approx 0$ ($R \approx R_T$), the following ligand and ligand/complex kinetics are obtained:

$$\frac{d}{dt^*} \begin{bmatrix} C^* \\ L^* \end{bmatrix} = \begin{bmatrix} -(1+\beta) & 1 \\ \gamma & -\gamma \end{bmatrix} \begin{bmatrix} C^* \\ L^* \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} u \quad (4)$$

where β and γ are given by

$$\beta = \frac{k_e}{k_{off}}, \gamma = \frac{K_a R_T}{N_{av} V_c} \quad (5)$$

3. STRUCTURE OF THE LIGAND/RECEPTOR INTERACTION NETWORK IN AGGREGATING DICTYOSTELIUM CELLS

We now show how a ligand/receptor interaction network displaying the generic structure given in the previous section may be extracted in a straightforward manner from a model for the complete network underlying cAMP oscillations in *Dictyostelium* published in [Laub and Loomis, 1998, Maeda et al., 2004], and shown in Figure 1.

The corresponding model consists of a set of nonlinear differential equations in the following form:

$$\begin{aligned}
\frac{d[\text{ACA}]}{dt} &= k_1[\text{CAR1}] - k_2[\text{ACA}][\text{PKA}] \\
\frac{d[\text{PKA}]}{dt} &= k_3[\text{cAMPI}] - k_4[\text{PKA}] \\
\frac{d[\text{ERK2}]}{dt} &= k_5[\text{CAR1}] - k_6[\text{PKA}][\text{ERK2}] \\
\frac{d[\text{RegA}]}{dt} &= k_7 - k_8[\text{ERK2}][\text{RegA}] \\
\frac{d[\text{cAMPI}]}{dt} &= k_9[\text{ACA}] - k_{10}[\text{RegA}][\text{cAMPI}] \\
\frac{d[\text{cAMPe}]}{dt} &= k_{11}[\text{ACA}] - k_{12}[\text{cAMPe}] \\
\frac{d[\text{CAR1}]}{dt} &= k_{13}[\text{cAMPe}] - k_{14}[\text{CAR1}]
\end{aligned} \quad (6)$$

where ACA is adenylyl cyclase, PKA is the protein kinase, ERK2 is the mitogen activated protein kinase, RegA is the cAMP phosphodiesterase, cAMPI and cAMPe are the internal and the external cAMP concentrations, respectively, and CAR1 is the ligand-bound cell receptor. The ligand-receptor interaction network for this model can be extracted as follows:

$$\frac{d}{dt} \begin{bmatrix} [\text{CAR1}(t)] \\ [\text{cAMPe}(t)] \end{bmatrix} = \begin{bmatrix} -k_{14} & k_{13} \\ 0 & -k_{12} \end{bmatrix} \begin{bmatrix} [\text{CAR1}(t)] \\ [\text{cAMPe}(t)] \end{bmatrix} + \begin{bmatrix} 0 \\ k_{11} \end{bmatrix} [\text{ACA}(t)] \quad (7)$$

Note that in the above, $[\text{CAR1}(t)]$, $[\text{cAMPe}(t)]$ and $[\text{ACA}(t)]$ are concentrations in units of μM , and k_{11} , k_{12} , k_{13} and k_{14} are reaction constants in units of $1/\text{min}$. To transform the unit of $\text{CAR1}(t)$ into the number of molecules, we use the relation, $C = [\text{CAR1}(t)]N_{av}V_c$, and hence derive the following:

$$\begin{aligned}
\frac{dC}{dt} &= -k_{14}[\text{CAR1}(t)]N_{av}V_c + k_{13}[\text{cAMPe}(t)]N_{av}V_c \\
&= -k_{14}C + k_{13}N_{av}V_cL
\end{aligned} \quad (8)$$

where $L = [\text{cAMPe}(t)]$. In addition,

$$\frac{dL}{dt} = -k_{12}L + k_{11}[\text{ACA}(t)] \quad (9)$$

With the normalised states,

$$\frac{dC^*}{dt^*} = -\frac{k_{14}}{k_{\text{off}}}C^* + \frac{k_{13}N_{av}V_c}{R_Tk_{\text{on}}}L^* \quad (10)$$

Then,

$$\frac{dC^*}{dt^*} = -\frac{k_{14}}{k_{\text{off}}}C^* + L^* \quad (11)$$

where $L^* = L^*K_L$ and $K_L = (k_{13}N_{av}V_c)/(R_Tk_{\text{on}})$. Note that K_L is multiplied by L^* to make the coefficient equal to one as in (4). Similarly,

$$\frac{dL^*}{dt^*} = -\frac{k_{12}}{k_{\text{off}}}L^* + u \quad (12)$$

This can be written in a compact form as:

$$\frac{d}{dt} \begin{bmatrix} C^* \\ L^* \end{bmatrix} = \begin{bmatrix} -\frac{k_{14}}{k_{\text{off}}} & 1 \\ 0 & -\frac{k_{12}}{k_{\text{off}}} \end{bmatrix} \begin{bmatrix} C^* \\ L^* \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} u \quad (13)$$

Comparing (13) with (4), we notice that there are some differences in the structures of the two equations. However, this is mainly because of the effect of the $k_{\text{off}}C$ term in (2). Under the reasonable assumption that the effect of $k_{\text{off}}C$ in (2) is negligible compared to the other factors, (4) can be rewritten as follows:

$$\frac{d}{dt^*} \begin{bmatrix} C^* \\ L^* \end{bmatrix} = \begin{bmatrix} -\beta & 1 \\ 0 & -\gamma \end{bmatrix} \begin{bmatrix} C^* \\ L^* \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} u \quad (14)$$

Then, the following relations are obtained:

$$\beta = \frac{k_{14}}{k_{\text{off}}}, \quad \gamma = \frac{k_{12}}{k_{\text{off}}}, \quad u = \frac{k_{11}K_L[\text{ACA}(t)]}{K_Dk_{\text{off}}} \quad (15)$$

Although the generic ligand-receptor interaction network structure certainly seems to be used by *Dictyostelium* cells in generating cAMP oscillations, it can be immediately seen that a profound difference also exists. Unlike (11), the effect of C^* to dL^*/dt is zero. Thus, the rate of dissociation of the ligand from the receptor is very low, i.e. once the cAMP ligand is caught by the CAR1 receptors, it is rarely released before being absorbed into the cell.

The values of the constants in the above equations are given as follows: $k_{11} = 0.7 \text{ min}^{-1}$, $k_{12} = 4.9 \text{ min}^{-1}$, $k_{13} = 23.0 \text{ min}^{-1}$, $k_{14} = 4.5 \text{ min}^{-1}$, $R_T = 4 \times 10^4$, [Bankir et al., 2002, Maeda et al., 2004], and $k_{\text{off}} = 0.7 \times 60 \text{ min}^{-1}$ and $k_{\text{on}} = 0.7 \times 60 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ [Ishii et al., 2004]. Hence, $\beta = 0.107$ and $\gamma = 0.117$.

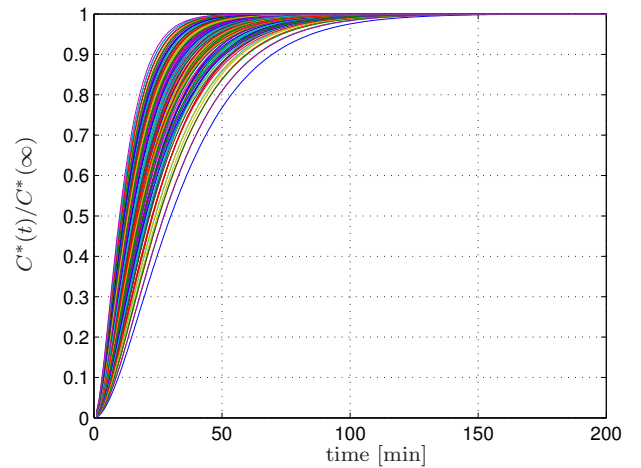


Fig. 3. Step responses with the perturbed parameters k_{12} and k_{14} . Each kinetic parameter is perturbed by up to $\pm 50\%$. The response is normalised by the value of each steady state.

In [Soll et al., 1976], the average diameter and volume of a *Dictyostelium* cell are given by $10.25 \mu\text{m}$ and $565 \mu\text{m}^3$. To calculate V_c , we consider an approximation for the shape of a *Dictyostelium* cell as a cylinder, as shown in Figure 2. Since the cell receptors are only distributed on the surface of the cell, the interior of the cell must be extracted to calculate an effective volume that represents the space where all molecular interactions occur under well-mixed conditions. The effective volume is determined such that the maximum number of ligand-bound CAR1 molecules is about 1% of the total number of receptors, to give a value of V_c equal to 1.66×10^{-16} liters. The simulation results shown in Figure 2 show the variation in the numbers of bound receptor molecules during cAMP oscillations, and were computed using a stochastic version of the Laub-Loomis model and Gillespie's direct method [Gillespie, 1977].

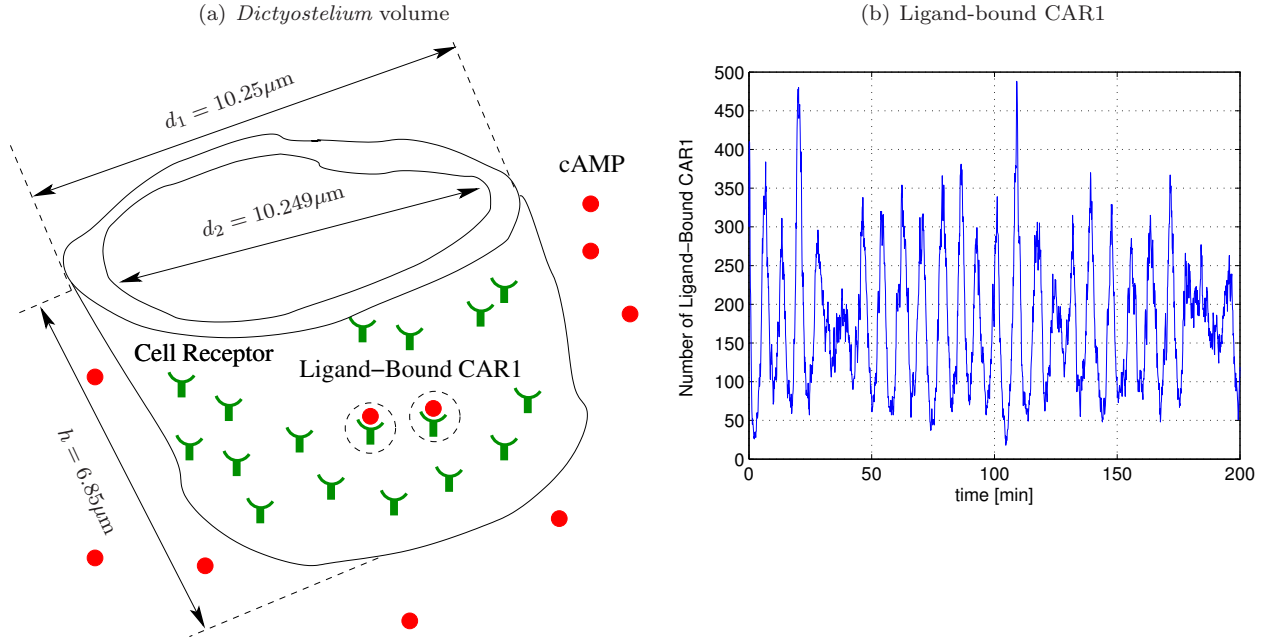


Fig. 2. *Dictyostelium* volume estimation: the effective volume is calculated as $\pi h(d_1^2 - d_2^2)/4$, where d_2 is adjusted such that the maximum number of ligand-bound CAR1 is approximately 1% of the total number of receptors.

4. OPTIMALITY AND ROBUSTNESS OF THE *Dictyostelium* LIGAND/RECEPTOR INTERACTION NETWORK

In this section we analyse the optimality and robustness of the parameters in the *Dictyostelium* ligand/receptor interaction network, from a Control Engineering perspective. Differentiating both sides of (11) with respect to the normalised time, t^* , we get

$$\begin{aligned} \frac{d^2 C^*}{dt^{*2}} &= \frac{-k_{14}}{k_{\text{off}}} \frac{dC^*}{dt^*} + \frac{dL^{**}}{dt^*} \\ &= \frac{-k_{14}}{k_{\text{off}}} \frac{dC^*}{dt^*} - \frac{k_{12}}{k_{\text{off}}} \left(\frac{dC^*}{dt^*} + \frac{k_{14}}{k_{\text{off}}} C^* \right) + u \end{aligned} \quad (16)$$

In a compact form, this can be written as

$$\ddot{C}^* + \frac{k_{12} + k_{14}}{k_{\text{off}}} \dot{C}^* + \frac{k_{12}k_{14}}{k_{\text{off}}^2} C^* = u \quad (17)$$

where the single and the double dot represent $d(\cdot)/dt^*$ and $d^2(\cdot)/dt^{*2}$, respectively.

Since the above equation is simply a second-order linear ordinary differential equation, we can define the natural frequency, ω_n , and the damping ratio, ζ as follows:

$$\ddot{C}^* + 2\zeta\omega_n\dot{C}^* + \omega_n^2 C^* = u \quad (18)$$

Comparing (17) with (18) we have that

$$\omega_n = \frac{\sqrt{k_{12}k_{14}}}{k_{\text{off}}}, \quad \zeta = \frac{k_{12} + k_{14}}{2\sqrt{k_{12}k_{14}}} \quad (19)$$

Substituting the appropriate values for the *Dictyostelium* network, we find that ω_n is equal to 0.112 and ζ is equal to 1.001. The overshoot, M_p , and the settling time, t_s , for a step input are given by [Franklin et al., 1994]

$$M_p = \begin{cases} e^{-\pi\zeta\sqrt{1-\zeta^2}}, & \text{for } 0 \leq \zeta < 1 \\ 0, & \text{for } \zeta \geq 1 \end{cases} \quad (20)$$

$$t_s = \frac{-\ln 0.01}{\zeta\omega_n} \quad (21)$$

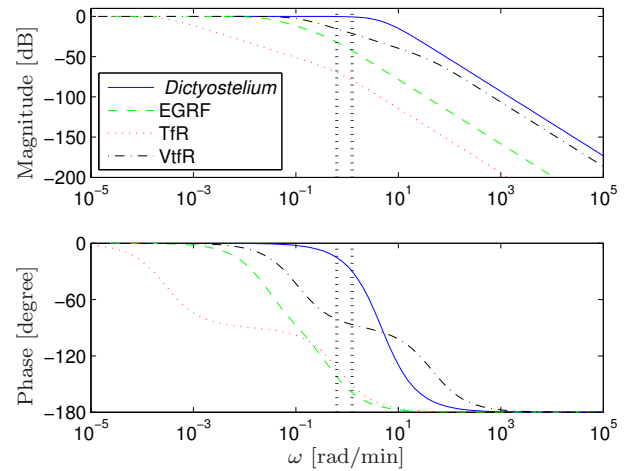


Fig. 4. Bode plots for the *Dictyostelium*, EGFR, Tfr and Vtfr networks, where the magnitude is normalised by the magnitude at the lowest frequency for comparison. The region inside the two dashed vertical lines corresponds to oscillations with periods between 5 and 10 mins, which is the range of cAMP oscillations observed experimentally in the early stages of aggregation of *Dictyostelium*.

Thus, the kinetics of the *Dictyostelium* ligand/receptor network produce a system with a damping ratio almost exactly equal to 1, i.e. the critical damping ratio. From the perspective of Control Engineering, the critical damping ratio is the optimal solution for maximising the speed of a system's response without allowing any overshoot:

$$\zeta^* = \arg \min J(\zeta) = t_s \quad (22)$$

subject to $M_p = 0$ and (17). Thus, it appears that *Dictyostelium* cells may have evolved a receptor/ligand interaction network which provides an optimal trade-off

Table 1. Kinetic parameters for EGFR, Tfr and Vtgr [Shankaran et al., 2007]

	k_e	k_{off}	K_a [1/M]	R_T	V_c
EGFR	0.15	0.24	$10^9/2.47$	2×10^5	4×10^{-10}
Tfr	0.6	0.09	$10^9/29.8$	2.6×10^4	4×10^{-10}
Vtgr	0.108	0.07	$10^9/1300$	2×10^{11}	4×10^{-10}

between maximising the speed of response and prohibiting overshoot of the response to external signals.

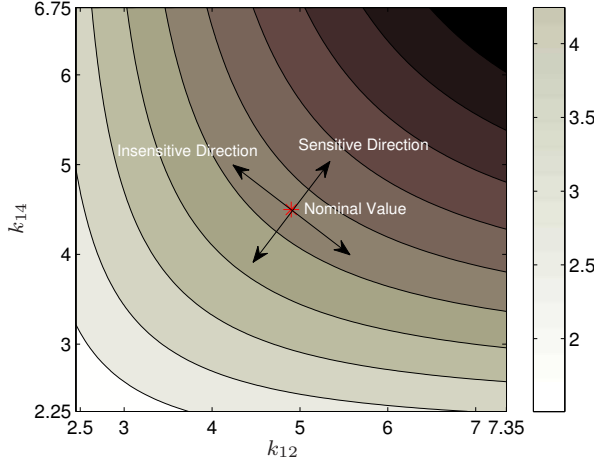


Fig. 5. Bandwidth variations for perturbations in the parameters k_{12} and k_{14} . Each kinetic parameter is perturbed by up to $\pm 50\%$. The nominal value is indicated by *. When k_{12} and k_{14} increase (decrease) simultaneously, the bandwidth change is maximised. When they are varied in opposite directions, the change in the bandwidth is minimised.

Using the generic structure for ligand/receptor interaction networks proposed in Shankaran et al. [2007], the speed of response of the *Dictyostelium* ligand-receptor kinetics may be compared with that of some other ligand-receptor kinetics, such as the epidermal growth factor receptor (EGFR), the transferrin receptor (Tfr) and the vitellogenin receptor (Vtgr). These receptors are involved in the development of tumours, the uptake of iron and the production of egg cells, respectively, see Jorissen et al. [2003], Rao et al. [1986], Li et al. [2003] for details. Using the definitions in (5) and the values given in Table 1, the damping factors for EGFR, Tfr and Vtgr may be calculated as follows: $\zeta_{EGFR} = 2.14$, $\zeta_{Tfr} = 24.68$ and $\zeta_{Vtgr} = 10.21$.

Thus, each of the above ligand-receptor kinetics, the responses are over-damped and thus the possibility of overshoot is completely prohibited. Indeed, in the case of the *Dictyostelium* network, the response cannot be under-damped for any combination of the kinetic parameters. This can be seen by considering the fact that

$$\zeta = \frac{k_{12} + k_{14}}{2\sqrt{k_{12}k_{14}}} \geq 1 \Rightarrow (k_{12} + k_{14})^2 \geq 4k_{12}k_{14} \quad (23)$$

$$\Rightarrow k_{12}^2 - 2k_{12}k_{14} + k_{14}^2 \geq 0 \Rightarrow (k_{12} - k_{14})^2 \geq 0$$

for all $k_{12} > 0$ and $k_{14} > 0$. Hence, the over-damped dynamical response appears to stem from the network structure itself, rather than being dependent on any particular values of the kinetic parameters. The step responses

with k_{12} and k_{14} perturbed by up to $\pm 50\%$ are shown in Figure 3. For this level of uncertainty in the kinetic parameters, the settling times vary between 35 min and 105 min (for the nominal parameter values the settling time is about 52 min).

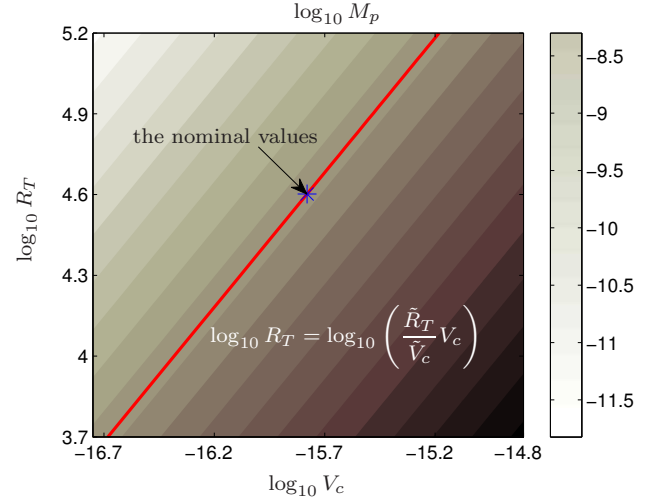


Fig. 6. Robustness of the maximum peak (M_p) of the impulse responses with respect to variations in the cell volume (V_c) and in the number of cell receptors (R_T): The number of cell receptors is likely to increase as the cell volume increases. The red-solid line is the feasible region if the cell volume and the number of cell receptors are varying while the density of the receptors, i.e. (the number of cell receptors)/(the cell volume), is constant. The nominal values, $\tilde{R}_T = 4 \times 10^4$ and $\tilde{V}_c = 1.66 \times 10^{-16}$, are indicated as *.

One significant difference between the *Dictyostelium* network and the other ligand-receptor networks considered above is its relatively fast response time. Since aggregating *Dictyostelium* cells exhibit oscillatory behaviour, rather than converging to a constant steady-state, the ligand/receptor interaction network may have evolved to maximise the speed of response, in order to ensure the generation of robust and stable limit cycles in the concentration of cAMP. This can be more clearly seen in the Bode plots for the responses of the different networks, which are shown in Figure 4. The bandwidth of the *Dictyostelium* ligand-receptor kinetics is about 3 rad/min, which is just above the minimum necessary to facilitate the oscillations in cAMP with a period of 5 to 10 min observed in *Dictyostelium* during chemotaxis. The change in the bandwidth of the network response with respect to parameter perturbations is shown in Figure 5. It is interesting to note that the bandwidth change is a maximum when k_{12} and k_{14} are simultaneously increasing or decreasing. On the other hand, if both parameters change asynchronously, the change in bandwidth is minimised. It is currently an open question as to which direction is indeed observed in nature and what the biological significance of such changes might be.

Finally, we recall that from the definition of $u(t)$,

$$u = \frac{k_{11}K_L[ACA(t)]}{K_Dk_{off}} = \frac{k_{11}k_{13}N_{av}}{k_{off}^2} \frac{V_c}{R_T} \quad (24)$$

the cell volume, V_c , and the total number of receptors, R_T , appear only in the definition of u in (17). Hence, variations in V_c and R_T can affect the static gain of the response but they have no effect on its dynamic characteristics. Moreover, it is most likely that the total number of receptors increases as the cell volume increases, i.e.,

$$\frac{V_c}{R_T} \approx (\text{constant}) \quad (25)$$

Under this assumption, even the static gain will be relatively insensitive to variations in the cell volume and in the number of receptors. This can be seen from Figure 6, which shows the maximum peak distribution for an impulse input, whose magnitude is given by $[ACA] = 0.01 \times 10^{-3} K_D \mu\text{M}$, with respect to different values of V_c and R_T . The red-line indicates the the major direction of V_c - R_T variations. Note that the maximum peak to the impulse input stays almost constant around the feasible line.

5. CONCLUSIONS

In this paper, the ligand/receptor interaction network of aggregating *Dictyostelium* cells was analysed from a Control Engineering perspective. The interaction network for this system was shown to exhibit a generic structure which appears to be highly conserved among many different kinds of organisms. For this structure, it appears that nature has engineered a set of network parameters which deliver robust and optimal performance, with respect to the relay of external signals into cellular transduction pathways. Specifically, it was shown that the set of kinetic parameters considered results in the fastest possible relay of external signals while allowing no overshoot in the response. Finally, we show that the response of the network to external signals is extremely robust to variations in the relevant kinetic parameters of the network, the cell volume and the number of receptors present on the surface of the cell.

ACKNOWLEDGMENTS

This work was supported by BBSRC research grant BB/D015340/1.

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