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Signal processing through a generalized module of adaptation and spatial sensingJ. Krishnan¹

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Signal transduction in many cellular processes is accompanied by the feature of adaptation, which allows certain key signalling components to respond to temporal and/or spatial variation of external signals, independent of the absolute value of the signal. We extend and formulate a more general module which accounts for robust temporal adaptation and spatial response. In this setting, we examine various aspects of spatial and temporal signalling, as well as the signalling consequences and restrictions imposed by virtue of adaptation. This module is able to exhibit a variety of behaviour in response to temporal, spatial and spatio-temporal inputs. We carefully examine the roles of various parameters in this module and how they affect signal processing and propagation. Overall, we demonstrate how a simple module can account for a range downstream responses to a variety of input signals, and how elucidating the downstream response of many cellular components in systems with such adaptive signalling can be consequently very non-trivial.

1 Introduction

Following the advent of molecular biology, an important focal point of biological research has been elucidating the regulation and interaction of networks of chemicals responsible for various cellular and genetic processes. This has led to the uncovering of highly complex networks involved in cell signalling in various important cellular processes (Alberts *et al.*, 2002), and also the extent to which these vary from organism to organism. While many aspects of the signalling circuitry in these systems have been uncovered, there are many other biochemical aspects which remain to be elucidated.

In many of these systems, making the transition from a network interaction diagram to understanding the signal transduction in a biochemical circuit is a very considerable challenge. While the lack of complete knowledge of all rate constants is a well recognized issue, there are many other factors which complicate the problem of elucidating signal propagation in a network, including the role of noise, history dependence, feedback, spatial variation and complex transport. In these systems there appear to be key features involved in the signal propagation.

One feature of signalling which is observed in a number of sensory transduction processes is adaptation, which roughly means that the nature of the response to some signal (spatial or temporal) somehow adjusts to account for the ambient strength of the signal at steady state. A striking example of adaptation occurs in bacterial chemotaxis (Berg, 2003) in *E. coli*. The bacterium *E. coli* responds to concentration of surrounding chemicals in a temporal manner and orchestrates its response to allow for it to move in more favourable directions (higher external concentrations). The response of a key protein (Che-Y) is necessary for controlling the flagellum in the bacteria to direct its motion. In order for the bacteria to respond reliably to temporal gradients, it is important for the response to depend on the temporal gradient as opposed to the absolute value of the external signal. Signal transduction in *E. coli* does indeed achieve this goal via a response which is independent of the absolute value of the external signal over five orders of magnitude (Berg, 2003). This is achieved by virtue of the fact that the key intermediate reaches a steady state independent of the absolute value of the external signal. This feature is an extremely important aspect of signalling in this system, and needs to be accounted for in any reliable quantitative description and understanding of the system. The fact that this adaptation is extremely robust has important implications for the kind of chemical interactions and signal flow to achieve this in the face of variability in parameters. A considerable body of modelling efforts is aimed at describing this adaptation process, along with other response characteristics (Tindall *et al.*, 2008). It is worth pointing that some models, such as

(Barkai and Leibler, 1997), are able to capture this adaptation process in a robust manner, independent of parameters (even though other characteristics of the response depend on parameters). A systems interpretation of the signalling network, and the discussion of an integral control mechanism underlying this network, responsible for robust adaptation, is discussed in (Yi *et al.*, 2000).

A specific example of adaptive signalling occurs in chemotaxis in *Dictyostelium* (in response to the ligand cAMP). Signal transduction occurs through the CAR1 receptor, and regulates phosphoinositide lipids such as $PI(3, 4, 5)P_3$ (representative of the cell compass response) along with other pathways. From experiments performed in cells immobilized with latrunculin (which allows for an easier study of signal transduction at the sensing stage of chemotaxis, decoupling it from cell motion) it was established that a spatially uniform stimulus of cAMP resulted in a transient response in $PI(3, 4, 5)P_3$ before returning to basal levels (and this feature was robust). Thus an increase in receptor occupancy still results in a downstream signalling component recovering to prestimulus levels. It was also established that this adaptation did not occur at the level of the receptor itself. Importantly in gradient experiments conducted on the same immobilized cells with the same ligand, the cells responded with a persistent spatially inhomogeneous response when the stimulus was in the form of a spatial gradient, and here at steady state the $PI(3, 4, 5)P_3$ response did not recover to basal levels. Thus signal transduction induced by cAMP and regulating the lipid $PI(3, 4, 5)P_3$ has the property of adaptation in spatially homogeneous stimuli, while resulting in a non-trivial and non-adaptive sensory response in a gradient stimulus (Parent and Devreotes, 1999). Both the response of the lipid $PI(3, 4, 5)P_3$ and in fact (as found subsequently) the enzyme PI3K share this property. Thus this setting provides an example where spatial sensory transduction is critical (and the chemotactic response relies critically on spatial signalling) and adaptive signal transduction occurs in response to homogeneous stimulation. The adaptive signalling to an important component of the cell compass allows the cell to respond robustly to ligand gradient signals with different mean values. Other examples of adaptive signalling and spatial response exist in this system.

A quantitative description of signal transduction in chemotaxis has to account for the above aspect of signalling. A simple model which accounts for adaptation in a robust way is the local excitation global inhibition model (LEGI) proposed by Levchenko and Iglesias (Levchenko and Iglesias, 2002). This model relies on the regulation of a fast excitatory pathway and a slower but highly diffusible inhibitory pathway, regulating a response element. The advantage of this model is that adaptation is achieved in a robust way. The fact that signal transduction to the response (compass lipid) in the experimental system is not purely local was convincingly demonstrated experimentally in (Janetopoulos *et al.*, 2004). Various aspects of

modelling in eukaryotic chemotaxis are discussed in (Iglesias and Levchenko, 2002; Krishnan and Iglesias, 2004; Dawes and Edelstein-Keshet, 2007; Iglesias and Devreotes, 2008). The basic module of adaptation coupled with spatial sensing is used in modelling signalling to various components in *Dictyostelium* (Ma *et al.*, 2004; Krishnan and Iglesias, 2007)

In this paper we study a more general framework of an adaptive mechanism involving an activatory element and an inhibitory element, either or both of which may be diffusible (or non-diffusible). Such a more general framework has not been examined before. This framework provides a useful setting in which the relation between adaptation and spatial responses may be investigated. It includes both the LEGI model (studied in (Levchenko and Iglesias, 2002; Krishnan and Iglesias, 2003; Krishnan and Iglesias, 2008)) as well as purely temporal adaptation mechanisms (such as ones similar to the cartoon model in (Othmer and Schaap, 1998)) as special cases. This framework is worth analyzing for different reasons. Firstly it provides insights into the nature of adaptive signal processing and connection between temporal and spatial signal transduction. Secondly, in this system, the existence of signal propagation through diffusible intermediates implies different possible roles of diffusive intermediates in signalling (activatory, inhibitory or both) in adaptive regulation of different components. Given the relative simplicity and generic features of the model, the results here will help elucidate other features of spatial and temporal signal transduction in other similar systems with adaptive signalling and spatiotemporal signal transduction.

This paper is organized as follows. In the next section, we formulate the module of adaptation mentioned above. In the following sections, we analyze various aspects of signal processing via this module: response to temporal stimuli, spatial stimuli and spatio-temporal stimuli. In particular we will carefully examine and characterize the roles of different parameters in this system, and the role they play in different aspects of signal transduction. We will use tools from systems dynamics/control to elucidate different aspects of signal transduction. We will also focus on what extent adaptation restricts the range of temporal and spatial responses of the module.

2 Model

The model consists of the receptor signal S regulating a response element R^* , located on the cell membrane. Both the receptor signal and hence any downstream response are in general dependent on spatial position. For a cell in the shape of a circular disc, the spatial location on the membrane is parametrized by the angle θ . The reaction from the inactive (R) to the active form of the response (R^*) is

regulated by the receptor signal by two parallel pathways: an activatory pathway involving an activator A and an inhibitor I both residing on the membrane (see Fig. 1).

Both the activator and the inhibitor are activated by the receptor signal in a linear fashion (see (Levchenko and Iglesias, 2002)). In this model both the activator and inhibitor diffuse on the cell membrane, in general at different rates (see schematic in Fig. 1(b)). The governing equations are:

$$\begin{aligned}
 \frac{\partial A}{\partial t} &= k_a S - k_{-a} A + k_{da} \frac{\partial^2 A}{\partial \theta^2} \\
 \frac{\partial I}{\partial t} &= k_i S - k_{-i} I + k_{di} \frac{\partial^2 I}{\partial \theta^2} \\
 \frac{\partial R}{\partial t} &= -k_f A R + k_r I R^* \\
 \frac{\partial R^*}{\partial t} &= k_f A R - k_r I R^*
 \end{aligned}
 \tag{1}$$

The above module is an input-output system with the input being the receptor occupancy signal (in dimensionless form) S which can depend on both angle and time, and the (dimensionless) output is R^* . The activator and inhibitor concentrations in dimensionless form are denoted by A and I . By adding the last two equations, we see that $R + R^*$ is constant throughout the dynamics, and we can assume the variables are suitably non-dimensionalized so that $R + R^* = 1$. This means the last two equations reduce to

$$\frac{\partial R^*}{\partial t} = k_f A (1 - R^*) - k_r I R^*
 \tag{2}$$

From above, the steady state of R^* is given by

$$R^* = \frac{A/I}{k_r/k_f + A/I}
 \tag{3}$$

When S is spatially homogeneous and non-zero the steady state concentrations of activator and inhibitor are given by $A = (k_a/k_{-a})S$ and $I = (k_i/k_{-i})S$, so that A/I and hence R^* are independent of S , thus guaranteeing adaptation in a robust fashion. We shall assume that the initial condition for all variables, for a given external degree of stimulus (assumed non-zero) correspond to steady state conditions.

We observe that the above model encompasses a range of different behaviour. When $k_{da}, k_{di} = 0$ we have a model of adaptation to all signals, similar to (Othmer and Schaap, 1998). When $k_{da} = 0, k_{di} \gg 1$

we have the original local excitation global inhibition model (formulated in (Levchenko and Iglesias, 2002) and also studied in (Krishnan and Iglesias, 2003)). When $k_{da} \gg 1, k_{di} = 0$, we have the local inhibition, global excitation model. When $k_{da}, k_{di} \gg 1$, we have a module transduces signals via strongly diffusible pathways. This is one aspect of the module. The other aspect pertains to which of the activatory and inhibitory processes is faster and which is slower. We will examine these different cases in detail.

3 Temporal signal processing

In this section, we will examine the kind of temporal signal processing possible from this module. Thus, the input S here is independent of θ and the signal propagation entirely results from the kinetics of the reactions. Examining this case in some detail is useful firstly because it gives insights into purely temporal signal transduction, and secondly it clarifies to what extent diffusion affects the range of signal processing.

As mentioned, the model by construction accounts for perfect adaptation in response to a homogeneous stimulus. While the steady state is independent of the external (homogeneous) concentration input, the transient response does depend on the stimulus as well as the kinetic parameters of the network. Intuitively we expect that whether the response exhibits a transient jump or dip depends on which of the two pathways, activatory or inhibitory, is regulated faster. A faster activator leads to a transient jump (as in the LEGI model initially proposed), while a faster inhibitor leads to a transient dip in response before adapting.

While all the kinetic constants k_a, k_{-a}, k_i, k_{-i} play a role in transient and steady state responses, which of the two pathways is faster (slower) is determined by the relative magnitudes of the degradation constants k_{-a}, k_{-i} . A faster activatory pathway corresponds to $k_{-a} > k_{-i}$ while a faster inhibitory pathway corresponds to $k_{-i} > k_{-a}$. This is easily seen as follows: defining scaled variables A_s, I_s as $A_s = (k_{-a}/k_a)A$ and $I_s = (k_{-i}/k_i)I$, we find that the equations for the scaled activator and inhibitor variables reads

$$\begin{aligned}\frac{dA_s}{dt} &= k_{-a}(S - A_s) \\ \frac{dI_s}{dt} &= k_{-i}(S - I_s)\end{aligned}\tag{4}$$

This indicates that the transient response of the scaled variables A_s, I_s is dependent on the kinetic constants k_{-a}, k_{-i} respectively. Whichever of these constants is higher determines which is the faster responding

pathway. Whether the response shows a transient jump or a dip depends on which of the two pathways responds faster. This is seen most transparently in the case where the reactions involving the regulation of the response (kinetic constants k_f, k_r) are much faster than the other reactions. In this case the reaction between R and R^* is essentially at a quasi-steady state and so

$$R^* = \frac{A/I}{k_r/k_f + A/I} \quad (5)$$

and so a faster activator implies that A/I increases before recovering to basal values, and this is reflected in a transient jump in response element R^* .

Having established when the response element exhibits a transient jump and when it exhibits a transient dip, a natural question to ask is if all ranges of concentrations of R^* can be reached by varying the receptor occupancy S . Since the receptor directly regulates the activator and inhibitor variables, this question involves establishing to what extent the input (S) can regulate the activator and inhibitor variables. The regulation equations for A and I can be cast in the form of a standard linear control system (Rugh, 1995) $dy/dt = Py + Qu$, where y is the vector of state variables and u is the vector of control variables. Here $y = [A, I]^T$, $u = S$, $P = \text{diag}(-k_{-a}, -k_{-i})$ and $Q = [k_a, k_i]^T$. A standard controllability analysis of this dynamical system indicates that the system is completely controllable (rank of controllability matrix = 2) indicating that the entire range of A, I values are accessible. However the range of activator and inhibitor values is restricted by the fact that the control input (receptor occupancy) S is restricted to be positive. In order to find the range of A/I , we directly examine its time derivative:

$$d/dt(A/I) = (1/I^2)(AI(k_{-i} - k_{-a}) + S(k_a I - k_i A)) \quad (6)$$

We can immediately conclude that if $k_{-a} > k_{-i}$ then A/I is bounded by k_a/k_i , since the time derivative of A/I at the surface $A/I = k_a/k_i$ is always negative. By exactly analogous reasoning, we can conclude that when $k_{-i} > k_{-a}$, then $A/I > k_a/k_i$ (in (Krishnan and Iglesias, 2008) we show that we can get arbitrarily close to these bounds). By writing the equation for R^* as

$$\frac{dR^*}{dt} = -(k_f A + k_r I)[R^* - (A/I)/(k_r/k_f + A/I)] \quad (7)$$

and noting the above bounds for A/I , we immediately have bounds for the response (from similar

reasoning): when $k_{-a} > k_{-i}$, we have $0 < R^* < k_a/k_i/(k_r/k_f + k_a/k_i)$, and when $k_{-i} > k_{-a}$ then $1 > R^* > k_a/k_i/(k_r/k_f + k_a/k_i)$.

Thus in each case we establish non-trivial bounds for the accessible values of R^* , explicitly in terms of various rate constants. The fact that the input signal S simultaneously regulates both the forward and reverse pathways in the regulation of R^* is responsible for these bounds. These bounds are valid for any admissible (positive) temporal variation of S , and in particular valid also for step inputs.

We thus conclude that in a homogeneous (step) stimulus, if $k_{-a} > k_{-i}$, a transient jump is observed, whose maximum amplitude is bounded by $k_a/k_i/(k_r/k_f + k_a/k_i)$, while when $k_{-a} < k_{-i}$, a transient dip is observed whose minimum value is bounded by this same factor. When $k_{-a} = k_{-i}$, then $A/I = k_a/k_i$ throughout the dynamics (from the equation for A/I), which implies that starting from a steady (basal) state, R^* remains at this basal state. This illustrates the fact that for certain parameter values, a homogeneous stimulus does not elicit any response, even if it is time varying. Fig. 2 shows simulations of different responses to homogeneous stimulation.

While the above analysis gives basic insights into which way the response will change in homogeneous stimulation, it does not give any information on the amplitude of the (transient) variation in a homogeneous stimulus of given magnitude. While simulating the network is very straightforward, understanding the amplitude of the response and how it depends on the magnitude of the stimulus is not so straightforward. Some basic analysis was performed in (Krishnan and Iglesias, 2008) by examining the case where the conversion between R and R^* is much faster than the regulation of activation and inhibition regulation by the receptor input signal. This allowed for an explicit description of different characteristics of the transient response in homogeneous stimulation.

In (Krishnan and Iglesias, 2008) it was shown that for a module subject to a change in external stimulus from level S_0 to level S at $t = 0$, the condition for an extremum in A/I (and hence R^* , assuming large k_f, k_r) is

$$(k_{-i} - k_{-a}e^{(k_{-i}-k_{-a})t})(1 + \beta e^{-k_{-i}t}) = -\beta k_{-i}(e^{-k_{-a}t} - e^{-k_{-i}t})$$

where $\delta := S_0/S$ and $\beta := \delta - 1$.

This transcendental equation can be solved numerically for the t value at which an extremum occurs. We see from above that it depends only on k_{-a}, k_{-i} and δ . Explicit analytical expressions and insight can be obtained for specific parameters. For example, when $k_{-a} = 2k_{-i}$, the point of of maximum deviation from the basal state can be solved explicitly, by effectively transforming the above equation into a quadratic

equation by setting $z := \exp(-k_{-i}t)$. The solution for z turns out to be (Krishnan and Iglesias, 2008)

$$z = \frac{1}{\delta^{1/2} + 1}$$

This indicates that the magnitude of the variable A/I at the time of maximum amplitude as well as the corresponding response are given by

$$\begin{aligned} A/I &= \gamma + \frac{\gamma(1 - \delta^{1/2})}{(1 + \delta^{1/2})} \\ R^* &= 1 - \frac{k_r/k_f}{k_r/k_f + 2\gamma/(1 + \delta^{1/2})} \end{aligned} \quad (8)$$

where $\gamma = k_a k_{-i} / k_i k_{-a}$. This depends on $k_r/k_f, \gamma$ and $\delta = S_0/S$. In particular, from the above expressions, we can conclude that for a large step input ($S_0 \ll S$) we see that A/I approaches $2\gamma = k_a/k_i$ which is the upper bound of A/I as derived above and correspondingly R^* approaches its upper bound of $k_a/k_i / (k_r/k_f + k_a/k_i)$. Likewise, in the case of a step decrease to nearly zero stimulus $S \ll S_0$, we find that A/I (and hence R^*) approaches the lower bound of 0.

In an exactly analogous way, for the case of a slower activator when $k_{-a} = k_{-i}/2$, we see that in the case of a homogeneous stimulus the value of A/I , when $S_0 \ll S$, approaches the lower bound of 0 (and likewise for R^*), and in the case of decrease in stimulus, with $S_0 \gg S$, A/I approaches its upper bound of k_a/k_i (with the corresponding upper bound for R^*). These results point to the more general fact that in the case of high stimulus, A/I approaches its upper or lower bound, according as whether $k_{-a} > k_{-i}$ or $k_{-i} > k_{-a}$.

4 Steady state spatial signal processing

The previous section focused on how the mechanism involved in adaptation placed important restrictions in the range of temporal signalling. The counteracting activatory and inhibitory steps combine to restrict the range of output signal in a non-trivial way. Further, we also saw that the relative magnitudes of the kinetic constants k_{-a}, k_{-i} , determined whether the response exhibited a transient jump or a transient depression before eventually returning to prestimulus levels. While the analysis gives insight into purely temporal signal processing, the response of this module to spatially inhomogeneous signals is of considerable interest, and this is what we discuss next.

We start by examining the steady state response to a static external gradient (linear external concentration field –usually referred to as a linear gradient) which translates to a signal $S(\theta) = a + b\cos\theta$,

where $|b| < |a|$. The steady state response for A and I is easily obtained via a Fourier series expansion: setting $A = A_0 + A_1 \cos\theta$, $I = I_0 + I_1 \cos\theta$, we find that at steady state:

$$\begin{aligned}
 A_0 &= (k_a/k_{-a})a \\
 A_1 &= (k_a/(k_{-a} + k_{da}))b \\
 I_0 &= (k_i/k_{-i})a \\
 I_1 &= (k_i/(k_{-i} + k_{di}))b \\
 R^* &= \frac{A/I}{k_r/k_f + A/I}
 \end{aligned} \tag{9}$$

We are now in a position to carefully examine the range of responses which can be obtained from this module, and which parameters affect these responses. For the response to act as cell compass and point essentially at the position of maximum concentration, the case of non-diffusing A, and highly diffusible I ($k_{da} = 0$, $k_{di} \gg 1$) was suggested leading to the well know Local Excitation Global Inhibition (LEGI) model. We first start by examining the response, and analyze the range of parameters for which a response analogous to a cell compass is obtained for such a simple static gradient. The dependence of R^* with A/I indicates that the maxima and minima of A/I correspond to those of R^* at steady state. From above the dependence of A/I on position is given by

$$A/I = \frac{(k_a/k_{-a})a + (k_a/(k_{-a} + k_{da}))b \cos\theta}{(k_i/k_{-i})a + (k_i/(k_{-i} + k_{di}))b \cos\theta} \tag{10}$$

By recognizing that the expression for A/I can be simplified as

$$A/I = A_1/I_1 - (1/I_1)(A_0I_1 - I_0A_1)/(I_0 + I_1 \cos\theta) \tag{11}$$

we see that the critical determinant of the maxima and minima of A/I is the term $A_0I_1 - A_1I_0$. In the case of a constant gradient, this term is obtained as

$$A_0I_1 - A_1I_0 = abk_a k_i [1/k_{-a}(k_{-i} + k_{di}) - 1/k_{-i}(k_{-a} + k_{da})] \tag{12}$$

We note from this, that the sign of the term does not—reassuringly—depend on the mean value or strength of the gradient of the external signal. It is however determined by the relative size of k_{di}/k_{-i} and k_{da}/k_{-a} .

Thus we see that when $k_{di}/k_{-i} > k_{da}/k_{-a}$, then the maxima of the response at steady state for such a signal coincide with that of the external signal, while, when $k_{di}/k_{-i} < k_{da}/k_{-a}$, the maxima of the external signal correspond to the minima of the internal response (and vice versa). Thus what this implies is that it is not the relative magnitudes of the diffusivities per se which is the determinant of the nature of the steady state response, but the relative magnitude of the diffusivities scaled by the corresponding degradation constant.

It immediately follows from above that when $k_{da} = 0$ (local activator), any diffusing inhibitor will necessarily give rise to a response whose steady state maximum matches that of the input for such a signal. This is a characteristic of the LEGI model. On the other hand if the inhibitor is non diffusing, while the activator diffuses, the maxima and minima of the response are opposite to that of the input signal.

We can draw various inferences from the result above for the case where both the activator and inhibitor diffuse, i.e. $k_{da}, k_{di} > 0$. Firstly we note that the above condition compares the diffusivities of each species scaled by their degradation constants. In particular, it implies that even if the diffusivities of both the activator and inhibitor are equal, a compass response analogous to chemoattractant gradient sensing is possible. In fact, even if the activator is more quickly diffusing than the inhibitor, such a response is possible. In general the difference in the magnitude of these two terms determines how strong the compass response is.

The above conclusion also suggests that in order to have a response from such a module tracking (essentially) the minimum of the external signal, it is necessary for the opposite inequality $k_{da}/k_{-a} > k_{di}/k_{-i}$ to hold good. In particular such a response can also occur with activator and inhibitor having equal (non-zero) diffusion coefficients, if the inhibitor degradation constant is faster than that of the activator.

The special case $k_{da}/k_{-a} = k_{di}/k_{-i}$ represents a set of parameter values which acts as a transition between these two cases. In this case, we find that for a gradient as above, the steady state response exhibits no spatial response at all, and is constant everywhere. This is indicative of a completely non-existent compass response to such a gradient at steady state. Different kinds of responses to steady state signals are seen in Fig. (3).

A special case of our network is one where both the activator and inhibitor are completely non-diffusible. This corresponds to the case where $k_{da} = k_{di} = 0$. Thus for this purely local signal transduction (a local excitation local inhibition model), the condition $k_{da}/k_{-a} = k_{di}/k_{-i}$ is trivially satisfied. Thus, not surprisingly, adaptation to homogeneous signals also implies adaptation to linear gradients and in fact adaptation to any spatial signals, since signal processing is purely local.

4.1 Steady state responses to gradients and responses to homogeneous stimulation

From the above and the previous section, we were able to determine the characteristics of the response in homogeneous stimulus as well as a constant gradient, and also the parameters which determine the response. For a homogeneous stimulus, the response exhibits a transient jump (H1) if $k_{-a} > k_{-i}$ (faster activator) and a transient depression (H2) if $k_{-a} < k_{-i}$ (faster inhibitor). No response (H3) in a homogeneous stimulus is observed if $k_{-a} = k_{-i}$. For the steady state response in a linear gradient, a response tracking the maximum of the external signal (SS1) is observed if $k_{da}/k_{-a} < k_{di}/k_{-i}$, and a response tracking the minimum of the external signal (SS2) is observed when $k_{da}/k_{-a} > k_{di}/k_{-i}$. A spatially uniform compass response (SS3) is observed when $k_{da}/k_{-a} = k_{di}/k_{-i}$.

From the above pieces of information, and noting the different parameters involved in each case, we can infer some interesting conclusions. The way this module responds to temporal inputs (such as step inputs) and the steady state response in constant gradients, is essentially independent. Thus it is possible to have any combination of homogeneous response H1/H2/H3 and any combination of steady state response in constant gradients (SS1/SS2/SS3). This indicates that the presence of such a module can lead to rather subtle spatial and temporal signal transduction by itself, and that one should be very careful about inferring spatial or temporal response from one another. In fact it also indicates that it is possible to have no temporal response in homogeneous stimulus, with a robust steady state compass response (SS1/SS2). It also indicates the possibility of a temporal response (H1/H2) with “adaptation” to linear gradients, as well as the possibility of no response in either homogeneous stimuli or at steady state to constant gradients. Figs 1 and 2 taken together, illustrate the different combinations of temporal and steady state spatial responses which can be attained (the temporal and spatial response for the case $k_{-a} = k_{-i}$ is not shown).

In particular a local excitation global inhibition model in the paper (Levchenko and Iglesias, 2002) corresponds to the combination of H1/SS1. The local inhibition global excitation model (LIGE) corresponds to SS2. A purely temporal adaptive signal processing corresponds to SS3, and can be regarded as a local excitation local inhibition model. Finally, a highly diffusible activator and inhibitor could provide any combination of responses, but a weak compass response is expected.

The role of the diffusivities of the activator and inhibitor in signalling can be further examined. We note that for a faster activator (H1) with highly diffusible inhibitor and non-diffusible activator (SS1), the

steady state of activator and inhibitor in a constant gradient are, respectively,

$$\begin{aligned} A &= (k_a/k_{-a})(a + b\cos\theta) \\ I &= (k_i/k_{-i})a + [k_i/(k_{-i} + k_{di})]b\cos\theta \end{aligned} \quad (13)$$

From here we see that the maximum of A/I (and hence the response) corresponds to $k_a k_{-i}/k_{-a} k_i (1 + b/a)$ when the inhibitor is highly diffusible $k_{di} \gg 1$. We note also that in homogeneous stimulation of any kind, A/I is constrained to lie in the range $(0, k_a/k_i)$. By examining the maximum of the steady state of the gradient response, we see that if $k_{-a}/k_{-i} < 2$, then for suitably strong gradients, it is possible for the maximum of the steady state response to exceed the absolute bounds established in temporal signalling. If we consider the case of local activator and diffusible inhibitor as above, with the difference that that the inhibitor is faster than the activator, then examining the minimum of the gradient response, we see that it can also fall below the lower bound set in temporal signalling. In fact in this case we have $k_{-i} > k_{-a}$ and $k_{di} \gg 1$, and the minimum of the response for a strong gradient ($b=a$) is essentially zero, clearly below the lower bound in temporal signalling of k_a/k_i . In this case, a sufficiently strong gradient is guaranteed to lead to a steady state response, which locally goes beyond the bounds set in temporal signalling. In each case, this further underscores the additional aspects brought to signalling by virtue of the diffusion of the inhibitor, and demonstrates in a precise way how this plays a role in expanding the range of signalling.

Parallel conclusions can be drawn in the case of a highly diffusible activator and non-diffusible inhibitor. In that case, the steady state of activator and inhibitor are

$$\begin{aligned} A &= (k_a/k_{-a})a + (k_a/(k_{-a} + k_{da}))b\cos\theta \\ I &= (k_i/k_{-i})a + (k_i/k_{-i})b\cos\theta \end{aligned} \quad (14)$$

When the diffusion of the activator is very high, then A/I approaches $k_a k_{-i}/k_{-a} k_i [a/(a + b\cos\theta)]$. Here again we see that for the case of a faster activator, it is possible for the maximum of the gradient response (located at the minimum of the external signal) to exceed the temporal bound of k_a/k_i . An exactly analogous conclusion can be made in the case of a slow activator, where the lower bound of k_a/k_i can be crossed by the minimum of the gradient response.

5 Observability of the module

Before we proceed to examine spatio-temporal signal processing in this module, we examine an issue pertaining to the input-output response. If one considers the receptor occupancy signal S as the input to the module and the response R^* as the output, a natural question arises as to whether this output (and its temporal variation) contains sufficient information from which to infer the state variables. In particular, a natural question is whether it is possible for different state variable values (A, I, R^*) for any admissible variation of inputs to give rise to the same observed output R^* ? If this were the case, the system with the output R^* would be regarded as unobservable with respect to the input.

We will show that for two systems exhibiting the same output (as a function of time) for any admissible temporal variation of inputs necessarily have the same state variables. We first examine the spatially homogeneous case. We suppose we have two systems (1 and 2) which at some instant have state variables $(A_1(0), I_1(0), R^*(0))$ and $(A_2(0), I_2(0), R^*(0))$. Suppose they have the same output $R^*(t)$ for any admissible variation of input. Then since the R^* (and hence derivatives) of the two state trajectories are equal, it follows from the equality of rate of change of R^* in the two cases that

$$k_f(1 - R^*)(A_1 - A_2) = k_r R^*(I_1 - I_2) \quad (15)$$

or in other words, assuming, without loss of generality that $I_1 \neq I_2$ that

$$(A_1 - A_2)/(I_1 - I_2) = k_r R^*/k_f(1 - R^*) \quad (16)$$

However the evolution of $A_1 - A_2$ can be directly tracked by subtracting the activator equations for the two trajectories, and likewise for $I_1 - I_2$:

$$\begin{aligned} d(A_1 - A_2)/dt &= -k_{-a}(A_1 - A_2) \\ d(I_1 - I_2)/dt &= -k_{-i}(I_1 - I_2) \end{aligned} \quad (17)$$

which reveals that whatever the variation of S , the difference in the two cases varies as:

$$\begin{aligned} A_1 - A_2 &= (A_1(0) - A_2(0))\exp(-k_{-a}t) \\ I_1 - I_2 &= (I_1(0) - I_2(0))\exp(-k_{-i}t) \end{aligned} \quad (18)$$

Thus we see that

$$(A_1 - A_2)/(I_1 - I_2) = (A_1(0) - A_2(0))/(I_1(0) - I_2(0))\exp((k_{-i} - k_{-a})t) \quad (19)$$

independent of the regulating signal! Now if $k_{-a} \neq k_{-i}$, we find that that by varying S , we can change the R^* variation, which will cause the ratio of difference in activators and inhibitors (which is a function of R^*) to generically differ for general input signals from the exponential variation of the formula above. This means that the only way in which two different systems give the same output for any admissible signals is if $I_1(0) = I_2(0)$ and $A_1(0) = A_2(0)$, which means that the two systems have identical state variables.

When $k_{-a} = k_{-i}$, we find from above that $(A_1 - A_2)/(I_1 - I_2) = (A_1(0) - A_2(0))/(I_1(0) - I_2(0))$ a constant. However in this case, R^* is a constant in the dynamics, and hence any variation of input doesn't change the output. Thus it is indeed possible for two different systems with different state variables to give the exact same output and the system in this case is unobservable.

The above argument can be essentially extended for the case of input signals with spatial and temporal variation. Here again, we can demonstrate that if two different systems yield the same output for all admissible variation of the input S (assumed smoothly varying), they should have the same state variables. Using the exact same notation as above (except that in this case all input and state variables have spatial variation as well), just as before the requirement that the output (R^*) of the two systems is equal implies that

$$(A_1 - A_2)/(I_1 - I_2) = k_r R^*/k_f(1 - R^*) \quad (20)$$

as a function of space and time. The evolution of the difference ($A_1 - A_2$ and $I_1 - I_2$) satisfies

$$\begin{aligned} d(A_1 - A_2)/dt &= -k_{-a}(A_1 - A_2) - k_{da} \frac{\partial^2(A_1 - A_2)}{\partial \theta^2} \\ d(I_1 - I_2)/dt &= -k_{-i}(I_1 - I_2) - k_{di} \frac{\partial^2(I_1 - I_2)}{\partial \theta^2} \end{aligned} \quad (21)$$

Both these equations can be easily solved by a Fourier series decomposition. The evolution of the differences $A_1 - A_2$ and $I_1 - I_2$ depends only on their initial values and system parameters and not on the input signal. In any case, we can see that by varying the input signal $S(\theta, t)$, the R^* will in general vary and not correspond to the value imposed above. This is, in fact, true even when $k_{-a} = k_{-i}$. Thus if two

systems have exactly the same output for all admissible variation of input, they must necessarily have the same state variable values.

6 Spatiotemporal signal transduction

In the previous sections, we examined how the module responds to purely temporal signals, including the extent to which the opposing pathways act to restrict the range of the output. By examining the steady state response to a static linear gradient we showed that the output can involve either a response whose maximum is coincident with the maximum of the input or one whose maximum is co-incident with the minimum of the input. The fact that varying various parameters allowed for any combination of response in homogeneous stimulation (a jump, depression or no response) and response in a gradient was also demonstrated.

While the above studies provide basic insight into how the module processes spatial and temporal signals, a basic question which arises is how the module responds to signals with simultaneous spatial and temporal variation. We examine these issues in this section. The questions which we address are: to what extent does adaptation affect the range of spatio-temporal signalling? Does the intuition obtained for response in a static gradient carry through for spatio-temporal signalling? What are the roles of the diffusivities of the activator and inhibitor?

In order to examine spatiotemporal signal processing in this module and make a useful comparison with the previous cases, we consider the response of the module to a temporally varying linear gradient – i.e. a linear gradient whose characteristics (mean value) and gradient can be varied temporally. Thus the receptor occupancy input is $S(\theta, t) = S_0(t) + S_1(t)\cos(\theta)$, where the magnitude of S_1 is always less than or equal to S_0 (and S_0 is always positive). We focus on the case where S_1 is always greater than or equal to zero, thereby not allowing a reversal in the gradient. In the network, the signal S regulates the output R^* only via its regulation of the activating and inhibitory pathways. By expanding the activator and inhibitor concentration profiles in Fourier modes, we have $A(\theta, t) = A_0(t) + A_1(t)\cos(\theta)$ and $I(t) = I_0(t) + I_1(t)\cos(\theta)$, we can easily write down evolution equations for the Fourier components:

$$\begin{aligned}
\frac{dA_0}{dt} &= k_a S_0 - k_{-a} A_0 \\
\frac{dA_1}{dt} &= k_a S_1 - (k_{-a} + k_{da}) A_0 \\
\frac{dI_0}{dt} &= k_i S_0 - k_{-i} I_0 \\
\frac{dI_1}{dt} &= k_i S_1 - (k_{-i} + k_{di}) I_1
\end{aligned} \tag{22}$$

This represents a linear control system (Rugh , 1995), with the control inputs given by S_0 and S_1 . The linear control system can be written in standard control engineering format $dx/dt = Px + Qu$, where x is the vector of state variables and u is the vector of control inputs. In the present case $x = [A_0, A_1, I_0, I_1]^T$, $u = [S_0, S_1]^T$ $P = \text{diag}(-k_{-a}, -(k_{-a} + k_{da}), -k_{-i}, -(k_{-i} + k_{di}))$ and $Q =$ is a 4 x 2 matrix with columns $[k_a, k_i, 0, 0]^T$, $[0, 0, k_a, k_i]^T$, $u = [S_0, S_1]^T$. Again a standard controllability analysis of this linear control system can be performed, and the rank of the controllability Gramian $[P|Qp|Q^2P|Q^3P]$ is found to be 4, indicating that the system is completely controllable. However the extent of accessibility of the state space is restricted by the restriction on the control inputs (positivity of S_0 and magnitude of S_1 less than or equal to S_0).

In order to examine the instantaneous spatial maxima and minima of the response, it is instructive to consider the case where the reactions regulating the response (rate constants k_r, k_f) are much faster than the regulation of the activator and the inhibitor. This allows us to infer important information about the response, by examining the ratio of activator and inhibitor concentrations.

In order to do this, we note the following. We consider the case where S_1 is always non-negative. This means that the direction of the gradient is not changed, although the steepness may be altered. $A/I = (A_0 + A_1 \cos\theta)/(I_0 + I_1 \cos\theta)$ and hence the maximum of A/I is either at $\theta = 0$ or $\theta = \pi$. Furthermore, the maximum is at $\theta = 0$ (co-incident with the maximum of the external signal) if $A_1/A_0 > I_1/I_0$ and at $\theta = \pi$ if $A_1/A_0 < I_1/I_0$. Now we proceed to examine when the above inequalities hold good.

Case (i) $k_{-a} + k_{da} < k_{-i} + k_{di}$ and $k_{-a} > k_{-i}$. By examining the expressions for A_0, I_0 and their regulation by a common controller S_0 , we can directly use our insight from purely temporal signalling (see earlier section) to conclude that $A_0/I_0 < k_a/k_i$. In this case similarly examining the regulation of the pair of variables A_1, I_1 by controller S_1 we conclude that $A_1/I_1 > k_a/k_i$ (the “deactivating” constant for A_1 is

less than that of I_1). Thus we find that $A_1/I_1 > A_0/I_0$ always and hence the A/I has a maximum always co-incident with the external signal. This thus corresponds to the case where the compass is able to track a temporally varying linear gradient with fidelity and provide a response whose maximum corresponding to that of the external signal.

Case (ii) $k_{-a} + k_{da} > k_{-i} + k_{di}$ and $k_{-a} > k_{-i}$. By examining the expressions for A_0, I_0 and their regulation by a common controller S_0 , we conclude that $A_0/I_0 < k_a/k_i$. In this case from the regulation of the pair of variables A_1, I_1 by controller S_1 we find that $A_1/I_1 < k_a/k_i$. Thus we are unable to conclude anything about the relative magnitudes of A_0/I_0 and A_1/I_1 , In fact we can construct simple examples where the difference between A_0/I_0 and A_1/I_1 changes sign during the dynamics (see below), and in this case, the maximum of the compass response is not guaranteed to be coincident with the maximum of the external signal.

The conditions above imply that for $k_{-a} > k_{-i}$ (fast activator), the contrast between diffusivities has to be sufficient to ensure that the maximum of the cell compass response is co-incident with the external signal in a linear gradient: $k_{di} - k_{da} > k_{-a} - k_{-i}$. It is interesting to compare this with the condition for the response maximum to be co-incident with the external signal maximum in a static linear gradient derived previously: $k_{di}/k_{-i} > k_{da}/k_{-a}$

From the two inequalities, it is easy to see that (for all positive kinetic constants and diffusivities) that if $k_{da} + k_{-a} < k_{di} + k_{-i}$, then $k_{di}/k_{-i} > k_{da}/k_{-a}$, when $k_{-a} > k_{-i}$. To see this (Fig. 4) we examine the two lines $k_{da} + k_{-a} = k_{di} + k_{-i}$ and $k_{di}/k_{-i} = k_{da}/k_{-a}$. In the $k_{da} - k_{di}$ space the second line is a line of slope less than 1 passing through the origin, whereas the first line is a line of slope 1, with a positive y-intercept, and hence they do not intersect in the positive quadrant. It immediately follows that the condition $k_{da} + k_{-a} < k_{di} + k_{-i}$ implies $k_{di}/k_{-i} > k_{da}/k_{-a}$, but not the other way around. In other words, the module which guarantees the tracking of maximum of linear gradients whose characteristics vary in time has a smaller parameter range than that where the static response tracks the maximum of the external signal.

Case (iii) $k_{-a} + k_{da} > k_{-i} + k_{di}$ and $k_{-a} < k_{-i}$. By examining the regulation of A_0, I_0 by a common controller S_0 (and similarly regulation of A_1, I_1 by S_1) we conclude that $A_0/I_0 > k_a/k_i$ and $A_1/I_1 < k_a/k_i$. Thus we find that $A_1/I_1 < A_0/I_0$ and hence the A/I has a minimum always co-incident with the maximum of the external signal. This thus corresponds to the case where the compass provide a response whose maximum tracks the minimum of the external signal in a temporally varying linear gradient

Case (iv) $k_{-a} + k_{da} < k_{-i} + k_{di}$ and $k_{-a} < k_{-i}$. By examining the regulation of A_0, I_0 by a

common controller S_0 (and likewise for regulation of A_1, I_1 by S_1) we conclude that $A_0/I_0 > k_a/k_i$ and $A_1/I_1 > k_a/k_i$. Here again, just as above, we are unable to conclude anything about the relative magnitudes of A_1/I_1 and A_0/I_0 and hence cannot conclude that the compass tracks the minimum.

Again just as above we find that the range of parameters for the maximum of the module to track the minimum of the external signal in a temporally varying linear gradient is less than that for a corresponding static gradient.

The previous results can be summarized in the two schematic graphs in Fig. 4 showing the diffusivity parameter space. In Fig. 4 (a) (which corresponds to $k_{-a} > k_{-i}$) in the positive quadrant, we see that the region above line 1 corresponds to the region where the maximum of the response corresponds to that of the external signal even for a temporally varying linear gradient, while the parameter region between the two lines corresponds to one where static responses are tracked with the response maximum co-incident with that of the external signal, without this property being preserved when the gradient is varied temporally. The region below line 2 is one where the response to static linear gradients is one where the maximum of the response is co-incident with the minimum of the external signal. Here again, in spatio-temporally varying signals, the instantaneous maximum of the internal response can either be coincident with the maximum or the minimum of the external signal. Fig 4(b) shows a similar picture for the case where $k_{-i} > k_{-a}$, where an essentially similar picture to Fig 4(a) is seen. There is a region of parameter space (below line 1) where the maximum of the response corresponds to the minimum of the external signal in both static and temporally varying linear gradients, and a larger region in parameter space (below line 2), where the maximum of the response tracks the minimum of the external signal for static gradients. This indicates how the response to spatiotemporally varying signals even with simple spatial profiles can be quite subtle and depend in a rather delicate manner on the various parameters.

Bounds on response We finally turn to the issue of whether, like in the case of purely temporal signalling, we can establish non-trivial bounds for the response of the module. In case (i), we have $k_{-a} > k_{-i}$ and $k_{-a} + k_{da} < k_{-i} + k_{di}$. Here, the maximum of the response is at $\theta = 0$ and the value of A/I here equals $A_0 + A_1/I_0 + I_1$. Since $A_1 < A_0$ and $I_1 > 0$, the response here is always less than $2A_0/I_0$ which, further, is always less than $2k_a/k_i$. This thus forms an upper bound for A/I and hence an upper bound for $R^* = 2k_a/k_i / (k_r/k_f + 2k_a/k_i)$. In this case the lower bound for R^* is 0, as seen from purely homegenous regulation.

In case (ii) $k_{-a} > k_{-i}$ but $k_{-a} + k_{da} > k_{-i} + k_{di}$. In this case, we still have a bound for

$A_0 + A_1/I_0 + I_1$ equalling k_a/k_i (since $A_0/I_0 < k_a/k_i$ and $A_1/I_1 < k_a/k_i$). However, we can no longer guarantee that the maximum is at $\theta = 0$. Furthermore, one cannot find a bound for the value of A/I at the other location of its possible maximum ($\theta = \pi$) independent of the diffusivities. In fact it is easy to see that if the inhibitor is completely non-diffusible, then for gradients where $S_0 = S_1$, then $I_0 = I_1$, and hence the A/I goes to infinity (resulting in response element concentration taking the value 1 here). Nevertheless as before, we can also assert a lower bound for A/I of 0, and also claim an upper bound for A/I (and a corresponding one for R^*) of k_a/k_i at the location $\theta = 0$.

Case (iii) occurs when $k_{-a} < k_{-i}$ and $k_{-a} + k_{da} < k_{-i} + k_{di}$. Here $A_0/I_0 > k_a/k_i$ and $A_1/I_1 > k_a/k_i$. Here again it is immediate to see that $A_0 + A_1/I_0 + I_1 > k_a/k_i$. However, just as in case (ii) we cannot guarantee that the minimum of A/I is at $\theta = 0$. In fact here, in the case of a completely non-diffusible activator, A/I can reach the value 0 at $\theta = \pi$ when $S_0 = S_1$. Hence there are cases where R^* may attain a value 0. Nevertheless, one can assert that the upperbound for R^* is 1, and also a lower bound for R^* at $\theta = 0$ of k_a/k_i .

Case (iv) $k_{-a} < k_{-i}$ and $k_{-a} + k_{da} > k_{-i} + k_{di}$. Here we have $A_0/I_0 > k_a/k_i$ and $A_1/I_1 < k_a/k_i$. Here the minimum of the response occurs at $\theta = 0$ and the corresponding value of A/I given by $A_0 + A_1/I_0 + I_1$ is always greater than $A_0/2I_0$ (since $A_1 > 0$ and $I_1 < I_0$), and hence A/I is always greater than $k_a/2k_i$. Thus in this case, we have a lower bound for $R^* = k_a/2k_i / (k_r/k_f + k_a/2k_i)$. The upper bound for R^* is 1 as is seen in the case of purely homogeneous signalling ($S_1 = 0$).

7 Response to spatial and temporal signals

We now discuss the response of this module to imposed homogeneous and gradient signals, in light of the results presented in the previous section extending some of the insights obtained there. Again, we base our analytical insights on the case where the reactions regulating R^* are much faster than those regulating A, I . In particular we will analyze what happens when the module is subjected to either a gradient, or homogeneous stimulation superimposed on a pre-existing gradient or simultaneous increases in the strength of the gradient and mean value of external concentration field.

The essential insights into the behaviour of the module are presented in Fig. 4 The essential insight is that the dynamical subsystem involved in regulating the variables A_0, I_0 and A_1, I_1 are similar in structure. Further, both result in the adaptation of the variable A/I in step changes of the input. The steady state value of A_0/I_0 when subject to a non-zero input S_0 is $k_a k_{-i} / k_i k_{-a}$, while the steady state value of

A_1/I_1 when subject to a constant input S_1 equals $k_a(k_{-i} + k_{di})/k_i(k_{-a} + k_{da})$.

We first consider the case when $k_{-a} > k_{-i}$ (see Fig. 5). Further suppose $k_{-a}/k_{da} > k_{-i}/k_{di}$. Note that this corresponds to the case where the maximum of the response in a static linear gradient is co-incident with the external signal maximum. Note from above that this precisely corresponds to the case where the steady state value of A_1/I_1 (which is independent of the stimulus S_1) is greater than the steady state of A_0/I_0 (which is independent of the stimulus S_0). Now we can consider two cases as before: (a) $k_{-a} + k_{da} < k_{-i} + k_{di}$. This implies that the steady state value of A_1/I_1 is greater than k_a/k_i and thus as mentioned before the value of A_1/I_1 is always constrained to be above k_a/k_i while that of A_0/I_0 is constrained to be below k_a/k_i . Thus the vertical “trajectories” of these two quantities never cross the same horizontal line at the same time. Thus the maximum of the response is coincident with the maximum of the external signal for any combination of step changes in S_0 and S_1 . (b) $k_{-a} + k_{da} > k_{-i} + k_{di}$. This means the steady state values of A_0/I_0 and A_1/I_1 are both below k_a/k_i . By looking at Fig. 5(b) we can now see conditions where the maximum of the response is not coincident with the instantaneous maximum of the external signal. This corresponds to the crossing of the trajectories of A_0/I_0 and A_1/I_1 past the same horizontal line at some instant. This immediately suggests scenarios in which this could happen. These include

(i) The case where the module is subject to a basal value of S_0 and S_1 . A step increase in S_0 of sufficient magnitude, keeping S_1 fixed, will result in the value of A_0/I_0 increasing transiently past the steady state of A_1/I_1 (note that an upper bound for A_0/I_0 is k_a/k_i and this is approached as the size of the step increases becomes very large). Thus for a change in S_0 the module will transiently, for a period of time, exhibit a response whose maximum is at the instantaneous minimum of the external signal. This is demonstrated in Fig. 6

(ii) The same as (i) except that there is a step increase in both S_0 and S_1 . A jump of sufficient magnitude in S_0 can still lead to the same scenario as before.

(iii) The same as (ii) except that there is a step increase in S_0 and step decrease in S_1 .

(iv) Keeping S_0 fixed, a step decrease in S_1 can lead to this. Note however that keeping S_0 fixed, a step increase in S_1 will never achieve this scenario.

It is worth pointing out also in the case of (ii) that this condition can be achieved even if the basal value of S_1 is zero. This is because, when S_1 is increased, A_1/I_1 decreases from k_a/k_i to reach its eventual steady state value.

Now suppose that $k_{-a}/k_{da} < k_{-i}/k_{di}$ (Fig. 5(c)). This corresponds to a response where the

maximum of the response coincides with the minimum of the external signal. Here the value of the basal level of A_1/I_1 is less than that of A_0/I_0 . Note that it necessarily follows that $k_{-a} + k_{da} > k_{-i} + k_{di}$. Here again a crossing can occur for example when S_0 is decreased keeping S_1 fixed, but also by keeping S_0 fixed (for suitable values of S_0) and increasing S_1 sufficiently. Thus transiently, for a period of time, the response of the module can exhibit a maximum co-localized with the maximum of the external signal. This is also evident by inspecting Fig. 5(c).

The case when $k_{-a} < k_{-i}$ can be analyzed in exactly the same way (by interchanging the role of activator and inhibitor), and is briefly discussed below. First we consider $k_{-a}/k_{da} < k_{-i}/k_{di}$. The basal level of A_0/I_0 in fixed S_0 is greater than that of A_1/I_1 in fixed S_1

Here we can examine the following scenarios:

(a) $k_{-a} + k_{da} > k_{-i} + k_{di}$. Here A_0/I_0 is always greater than k_a/k_i while A_1/I_1 is always less than this value, and no simultaneous crossing can occur. Hence even in dynamic variation of mean value and gradients the maximum of the response is coincident with the minimum of the external signal.

(b) $k_{-a} + k_{da} < k_{-i} + k_{di}$. Here exactly as in previously examined cases a crossing can occur, either by a sufficient step increase in S_0 keeping S_1 fixed, a sufficient increase in S_0 along with a step increase (or decrease) in S_1 , and even keeping S_0 fixed and decreasing S_1 .

If $k_{-a}/k_{da} > k_{-i}/k_{di}$, then this corresponds to the case where the response in a static gradient has a maximum co-incident with that of the external signal in a linear gradient. This means that the basal value of A_0/I_0 for fixed non-zero S_0 is lower than that of the basal value of A_1/I_1 for fixed non-zero S_1 . Here a crossing scenario can occur again decreasing S_0 keeping S_1 fixed, but also by keeping S_0 fixed and increasing S_1 sufficiently.

7.1 Responses to other signals

In this subsection, we briefly consider the response of the module to other signals. We first consider the response of the module to symmetric signals (symmetric with respect to a particular axis, in this case $x = 0$). Thus we examine an input signal of the form $S = S_0(t) + S_2(t)\cos(2x)$. Just as before, we can obtain the activator and inhibitor responses by decomposing them into Fourier series:

$A = A_0 + A_2\cos(2x)$, $I = I_0 + I_2\cos(2x)$. This results in the different equations for the Fourier modes

exactly as before:

$$\begin{aligned}
 \frac{dA_0}{dt} &= k_a S_0 - k_{-a} A_0 \\
 \frac{dA_2}{dt} &= k_a S_2 - (k_{-a} + 4k_{da}) A_2 \\
 \frac{dI_0}{dt} &= k_i S_0 - k_{-i} I_0 \\
 \frac{dI_2}{dt} &= k_a S_2 - (k_{-a} + 4k_{di}) I_2
 \end{aligned}
 \tag{23}$$

This determines the evolution of the Fourier modes. We notice that the structure of these equations is very similar to that of the case of a linear gradient, except that here the factor 4 appears along with the diffusion coefficients in the equations for the evolution of A_2, I_2 .

When the inputs S_0, S_2 are constant, at steady state, the ratio of activator to inhibitor is given by

$$\frac{A}{I} = \frac{(k_a/k_{-a} S_0 + k_a/(k_{-a} + 4k_{da}) S_2 \cos(2x))}{(k_i/k_{-i} S_0 + k_i/(k_{-i} + 4k_{di}) S_2 \cos(2x))}
 \tag{24}$$

From this one can immediately deduce conditions under which the maximum of the internal response coincides with that of the external signal. For specificity, we consider the case $k_{-a} > k_{-i}$. Other cases are analyzed exactly as before. The condition that the maximum of A/I coincides with the maximum of the external signal ($\theta = 0, \pi$) is given by

$$4k_{da}/k_{-a} > 4k_{di}/k_{-i}
 \tag{25}$$

This leads to exactly the same condition as that when the input is a linear gradient. Thus a range of parameters which leads to a response maximum coincident with signal maximum in a linear gradient, also leads to the same situation in this case of this bi-modal signal. If this inequality is violated, then the response has a maximum co-localized with the minima of the input signal ($\theta = \pi/2, 3\pi/2$).

If we examine the case where both S_0 and S_2 vary with time, and examine the condition for the response maximum to be co-localized with the instantaneous maximum, we find the required condition to be

$$k_{-a} + 4k_{da} < k_{-i} + 4k_{di}
 \tag{26}$$

This is a less conservative requirement (for the difference in diffusion coefficients of inhibitor and activator) than the corresponding case for a linear gradient. Thus if the corresponding situation was guaranteed in the case of linear gradient, it would also be guaranteed for such a signal, but not the other way around. Thus we can augment the diagrams presented earlier, by including this extra line. We thus obtain 4 regimes (see Fig. 7): in the first we have dynamic tracking of the maximum for both linear and bi-modal signals, in the second, we have dynamic tracking of bi-modal but not linear signals, in the third we have no guarantee of dynamic tracking for linear or bi-modal signals but guaranteed static tracking, and in regime 4, the maximum of the response is not even co-localized with the input signal maximum even in static response. The lack of dynamic tracking in regime 3 to bi-modal signals can also be obtained by imposing step changes of S_0 and/or S_2 similar to the previous section. Similar diagrams can be obtained for other parameter regions.

The above results have implications for the response of the module to a combination of linear gradients and bi-modal signals, but we do not discuss that here.

8 Conclusions

Adaptation, the process by which levels of key signalling intermediates are reset or readjusted according to levels of external stimuli (or other upstream signalling components) is observed in widespread contexts in cellular signalling, especially in sensory signal transduction (Fain *et al.*, 2001). This allows the response of the cell/signalling pathway to “filter out” background levels of the external stimulus, allowing the pathway to produce a response which depends on key characteristics of the stimulus (temporal gradient, spatial gradient) independent of the background signal strength. Examples of this process abound and include bacterial and eukaryotic chemotaxis. In these cases, the capability of a cell to respond to gradients in a sensitive way, over wide ranges of absolute levels of stimuli is critical. Adaptation in these systems has been found to be robust over wide ranges of absolute levels of external stimuli. From a modelling and systems perspective, adaptation is an important feature of signal propagation through biochemical pathways. It is of interest to examine what network structures, interactions and characteristics allow for such a feature. An important aspect is the robustness of adaptation and whether or not models can capture the adaptation property independent of parameter values.

In this paper we examined a module of adaptation, which generalizes a model developed (Levchenko and Iglesias, 2002) to capture robust perfect adaptation in eukaryotic chemotaxis in *Dictyostelium*. Here

we consider a more general version of that module, where we allow both the activator and inhibitor to be diffusible, and also for the regulation of either of these entities to be faster. This is useful for various reasons. Firstly it is useful in understanding signalling and adaptation to both specific “frontness” and “backness” components of the chemotaxing cell. It provides important insights into how different kinds of temporal adaptive and spatial behaviour may be captured. Secondly it provides a unified perspective from which key features of the activating and inhibiting pathways (reaction rates, diffusivities) can be understood, by varying parameters. Analyzing this framework provides insights into the extent to which temporal and spatial responses may be correlated. Finally, this setting is very useful for understanding how the adaptive behaviour arising from the interplay of two counteracting pathways can also lead to restrictions into the range of signalling and downstream response. The rather generic features of the module involving counteracting pathways involved in spatial and temporal signal transduction indicate that many insights obtained here may be relevant for other systems with adaptive signal processing.

Our aim was to carefully characterize spatial and temporal signal processing and input-output properties of this module. The transient response of the module when subject to a homogeneous step change in input involves an increase above basal levels if the degradation rate constant for the activator (k_{-a}) is greater than that of the inhibitor (k_{-i}) and involves a decrease in the opposite case. If the degradation rate constants are equal, the module exhibits no change in spatially homogeneous stimulation. The common regulation of opposing reactions by the external signal results in a non-trivial upper bound for the response in the case $k_{-a} > k_{-i}$ and a non-trivial lower bound when $k_{-a} < k_{-i}$.

We then examined the response of the module to simple static signals such as a linear gradient. In such a static gradient the response of the module has maximum co-incident with the maximum of the external signal if $k_{da}/k_{-a} < k_{di}/k_{-i}$, where k_{da} , k_{di} are the diffusivities of the activator and inhibitor. Such behaviour is representative of a frontness component in chemoattraction (with adaptive signalling). On the other hand in the case of the opposite inequality the maximum of the response is always co-incident with the minimum of such an external signal. This behaviour is representative of a frontness component in chemorepulsion or a backness component in chemoattraction. The difference in the magnitudes of these two quantities is proportional to the amplitude of the output. If the two quantities are equal, no gradient response is elicited in a linear gradient.

We showed that by a suitable choice of degradation constants and diffusivities, it is possible to have any combination of responses to homogeneous stimulation (increase, decrease, no response) transiently, and any combination of static response in a linear gradient (co-aligned maxima, counter-aligned maxima,

no gradient response). We show that in certain cases, response values in a gradient even at steady state can exceed the bounds of those achievable in temporal signalling. Thus one should be very careful in trying to correlate homogeneous and gradient responses in systems with such adaptive behaviour. This is important in trying to understand the dynamics of different signalling components in such processes and emphasizes the need to carefully experimentally monitor the response of these components to a variety of stimuli.

An analysis of how the module processed spatiotemporal signals such as linear gradients whose gradient strengths could change with time reveals that the dynamic variation of the gradient strength could result in a response whose maximum can “switch” from being aligned to the maximum to being aligned to the minimum of the external signal if the inequality $k_{da} + k_{-a} < k_{di} + k_{-i}$ is violated. It should be noted that this inequality provides a stronger constraint, than the inequality for the static linear gradient above, $k_{da}/k_{-a} < k_{di}/k_{-i}$. It should be emphasized that while the strength of the gradient in the above analysis was varied, the direction of the gradient was not varied. Obviously if the direction of the gradient is abruptly changed, there would necessarily be some time lag before the maximum of the response could track that of the signal, if at all. The above studies were further reinforced with studies of module response to a combination of homogeneous and gradient signals as well as bi-modal inputs. In certain parameter regimes we also established bounds on the response in spatially and temporally varying signals. Finally we also examined the issue of observability of the module. We showed that in purely temporal signals as long as $k_{-a} \neq k_{-i}$, then the system was observable in the sense that if two different systems exhibited the same output for all variations of the input, they necessarily had to have the same state variable values.

The above analysis provides a unified perspective from which to get some basic insights into spatial and temporal signal processing with adaptation. While the basic module is relevant to signalling in Dictyostelium, the basic nature of the module— involving a dynamic interplay between an activatory and an inhibitory process to ensure adaptation— implies that important insights can be transferred to other adaptive processes. The subtlety of spatial and temporal processing even in such a simple module has been demonstrated. The feature of adaptive signalling has important and non-trivial implications for how spatial and temporal signals are processed in such networks. The study above suggests that by changing different parameters (even just kinetic parameters) it is possible to alter the response to some or all of the inputs-temporal, spatial and spatiotemporal. This has important implications. It means that inhibiting some pathway involved in adaptive signalling, can have completely different effects on signal transduction from what may naively be expected. It also suggests that other external or internal chemical factors could themselves modulate or completely alter the signal transduction in very subtle ways in different contexts.

The simplicity of the module, as well as the insights resulting from the above study, point to potential applications of this study in synthetic biology. The feature of adaptation being of central importance in various biological sensing processes, it is very conceivable that this very same property could be employed intelligently in synthetic biological circuits involving spatial sensing. The results in the above study would provide the basis for designing artificial adaptive signalling circuitry with spatial signal processing.

While the studies here characterize the response of such a module to relatively simple inputs, further work must be done to understand the response of such a module to complex inputs. This is needed to better understand the role of adaptation in spatial and temporal signal transduction. Typically signal processing in many such systems also involve thresholds, saturation and feedback, to name a few elements. These elements could serve to strongly amplify or accentuate the differences in static/dynamic behaviour observed here, or interact with the adaptive signalling in a very non-trivial way. We will systematically examine the roles of these elements subsequently. In fact in such cases, the range and subtlety in the overall behaviour could have its origin in the range of dynamic behaviour analyzed here. The coupling of such adaptive behaviour with downstream signalling can also be examined carefully. More generally the consequences of having adaptive signal processing as part of information propagation is worth examining carefully.

In summary, it is worth stating that while the obvious biochemical complexity involved in cellular signal transduction is well known, the complexity in signal propagation through biochemical circuits should not be underestimated. The roles of signal processing become apparent in processes such as adaptation and analysis from a systems perspective coupled with biochemical and experimental investigations provide a way of unravelling (and potentially also artificially constructing) interesting signal processing realized by natural biochemical circuits with important consequences.

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Fig. 1. Schematic of model network (a) The reaction network depicting the regulation of an activator A and an inhibitor I by the external signal, both of which regulate in parallel, the conversion between R and R^* . The response element R^* is the output of the module. (b) The wiring diagram of (a) contains no spatial information. The schematic in (b) indicates that the signal transduction to the elements A and I could have very different spatial characteristics. This is another aspect of the parallel (and opposing) regulation of the response element by the activator and the inhibitor. (c) The model is postulated on the membrane of a cell, idealized as a circular disc. This results in the model being postulated on a one-dimensional domain, with periodic boundary conditions.

Fig. 2. Processing of purely temporal signals. The module responds to homogeneous stimulation with either a transient jump (when $k_{-a} > k_{-i}$) seen in (a) or with a transient dip (when $k_{-i} > k_{-a}$) seen in (b), before returning to basal levels. Parameter values for (a) are $k_a = k_{-a} = 1.0, k_i = k_{-i} = 0.2, k_r = 2, k_f = 2$. This response is independent of the diffusivities. Stimulation is changed from a basal value of $S = 0.2$ to $S = 2$.

Fig. 3. Steady state response to gradients This figure shows the responses of the module to a linear gradient $S(\theta) = 2.0 + 1.0\cos\theta$. The response is plotted as a function of position θ (which varies from 0 to 2π). Case (a) corresponds to faster activator, and more strongly diffusible inhibitor $k_a = k_{-a} = 1.0, k_i = k_{-i} = 0.2, k_r = 2, k_f = 2, k_{da} = 0.1, k_{di} = 1.0$. Case (b) corresponds to faster activator, and more strongly diffusible activator $k_a = k_{-a} = 1.0, k_i = k_{-i} = 0.2, k_r = 2, k_f = 2, k_{da} = 1.0, k_{di} = 0.1$. Case (c) corresponds to faster inhibitor, and more strongly diffusible inhibitor $k_a = k_{-a} = 0.2, k_i = k_{-i} = 1.0, k_r = 2, k_f = 2, k_{da} = 0.1, k_{di} = 1.0$. Case (d) corresponds to faster inhibitor, and more strongly diffusible activator $k_a = k_{-a} = 0.2, k_i = k_{-i} = 1.0, k_r = 2, k_f = 2, k_{da} = 1.0, k_{di} = 0.1$. Cases (a) and (c) result in a response co-incident with the maximum of the external signal, while cases (b) and (d) result in a response whose maximum is co-incident with the minimum of the external signal. Case (e) represents a situation where a homogeneous response is seen in response to a linear gradient (see text). Parameter values are $k_a = k_{-a} = 1.0, k_i = k_{-i} = 0.2, k_r = 2, k_f = 2, k_{da} = 0.5, k_{di} = 0.1$.

Fig. 4. Regions in diffusivity space corresponding to differing responses to linear gradients Case (a) shows the case of a faster activator $k_{-a} > k_{-i}$. Line 2: $k_{da}/k_{-a} = k_{di}/k_{-i}$ separates two regions with different steady state responses of the module to linear gradients. Line 1: $k_{di} + k_{-i} = k_{da} + k_{-a}$

separates two regions with different behaviour to linear gradients whose characteristics may vary in time. Case (b) shows these same lines for the case of a faster inhibitor $k_{-i} > k_{-a}$.

Fig. 5. Different scenarios corresponding to steady states of A_0/I_0 and A_1/I_1 (see text) This figure examines the case of a faster activator $k_{-a} > k_{-i}$. The relative positions of steady states of A_0/I_0 (full line) and A_1/I_1 (dotted line) which are both independent of mean value and gradient strength of a linear gradient, relative to k_a/k_i (dashed line), which is an upper bound of A_0/I_0 in any temporally varying linear gradient or homogeneous signal. Changes in mean value or strength of gradient involve transient changes in A_0/I_0 and A_1/I_1 from their basal values, and may be viewed as vertical trajectories parametrized by time. Case (a), corresponds to $k_{-a} + k_{da} < k_{di} + k_{-i}$. In response to any temporally varying linear gradient, the value of A_0/I_0 moves vertically relative to its basal level, but is always less than k_a/k_i . The value of A_1/I_1 changes vertically but always remains above k_a/k_i . Thus at no instant of time can the “trajectories” of these two cross the same horizontal line. This implies that there can be no transient reversal of orientation in temporally varying linear gradients (see text). In cases (b) and (c), these steady state values lie on the same side of k_a/k_i and hence situations can occur where these quantities can temporally cross the same horizontal line at some instant of time, signalling a reversal in orientation of maximum of the response. See text for more details.

Fig. 6. Temporary reversal of maximum/minimum of response in temporally varying linear gradient

A cell initially at a steady state response to a basal gradient of $S = 0.2 + 0.2\cos\theta$ is subject to a homogeneous stimulation superimposed upon a gradient, leading to it being subject to a signal $S(\theta) = 2 + 0.2\cos\theta$ at $t=0$. The final steady state response is shown in (a) with a response whose maximum co-incides with that of the external signal. However at an intermediate time $t = 2$, the response is one, whose maximum co-incides with the minimum of the external signal. A plot of the response of the cell at $\theta = 0$ (dash-dotted line) and $\theta = \pi$ (full line) which are the locations of the cell in contact with the maximum and minimum of the external signal clearly demonstrates the crossing of these trajectories in time.

Fig. 7. Regions in diffusivity space corresponding to differing responses to bi-modal inputs This figure shows the line $k_{di} + k_{-i}/4 = k_{da} + k_{-a}/4$ (dashed line) which separates regions of diffusivity space into regions with different responses to temporally varying bi-modal signals. This is superimposed on Fig. 4. The line which separates different steady state response to bi-modal signals,

is still the line $k_a/k_{-a} = k_{di}/k_{-i}$.

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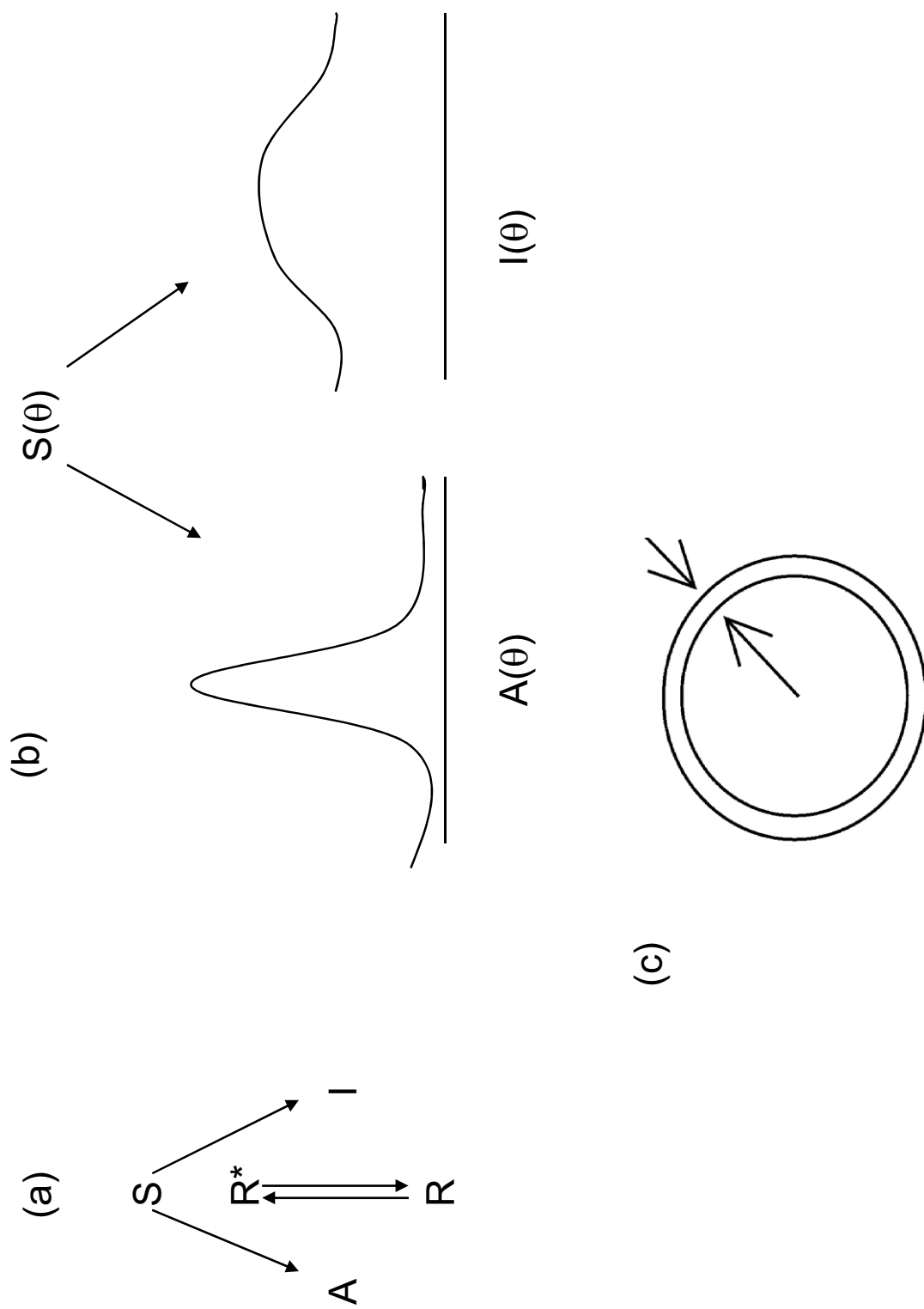
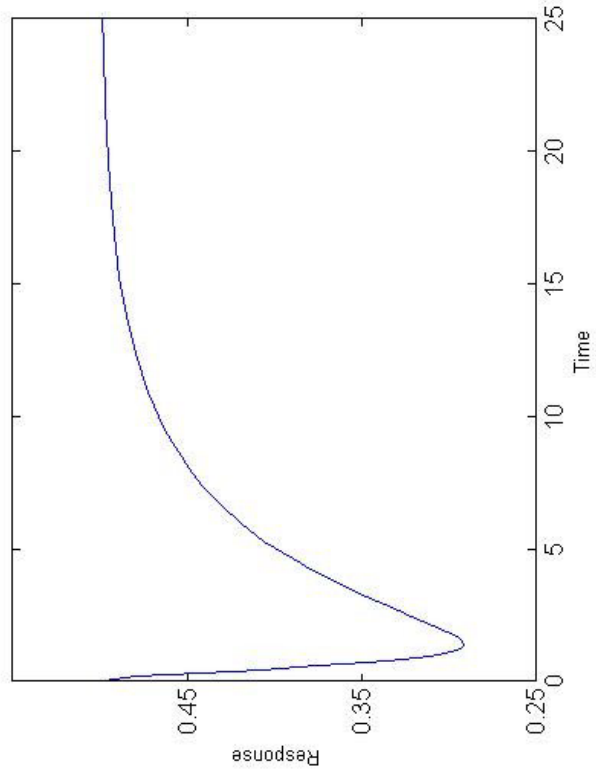
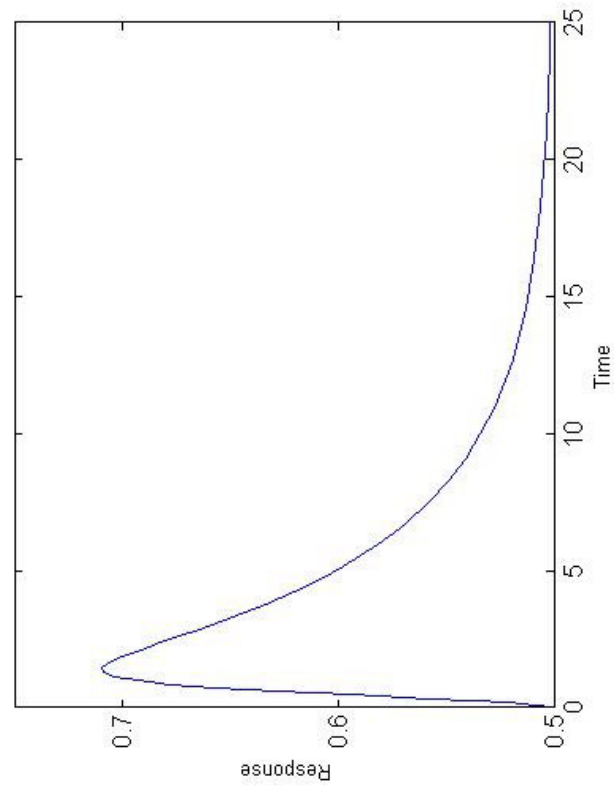


Fig. 1



(a)



(b)

Fig. 2

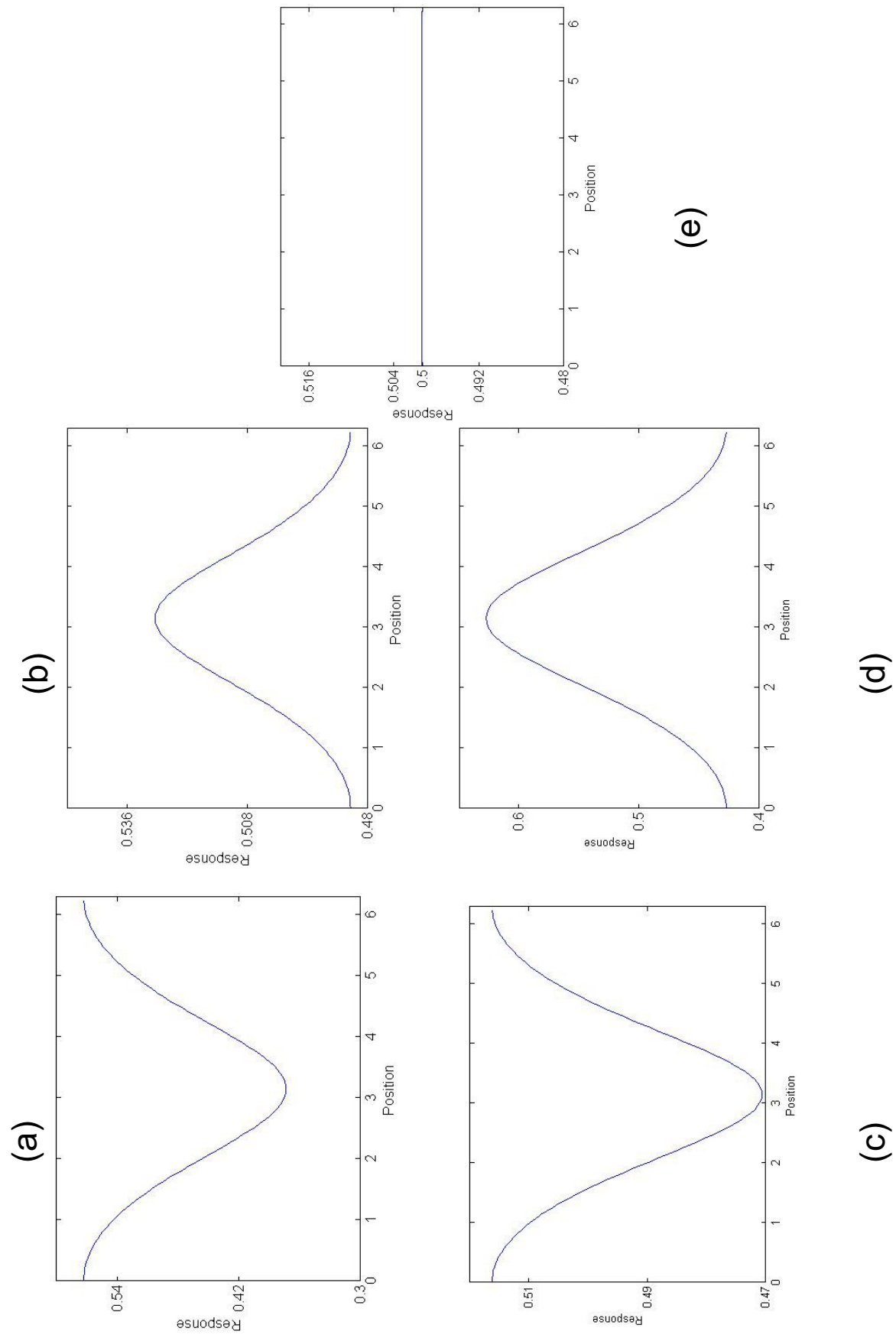
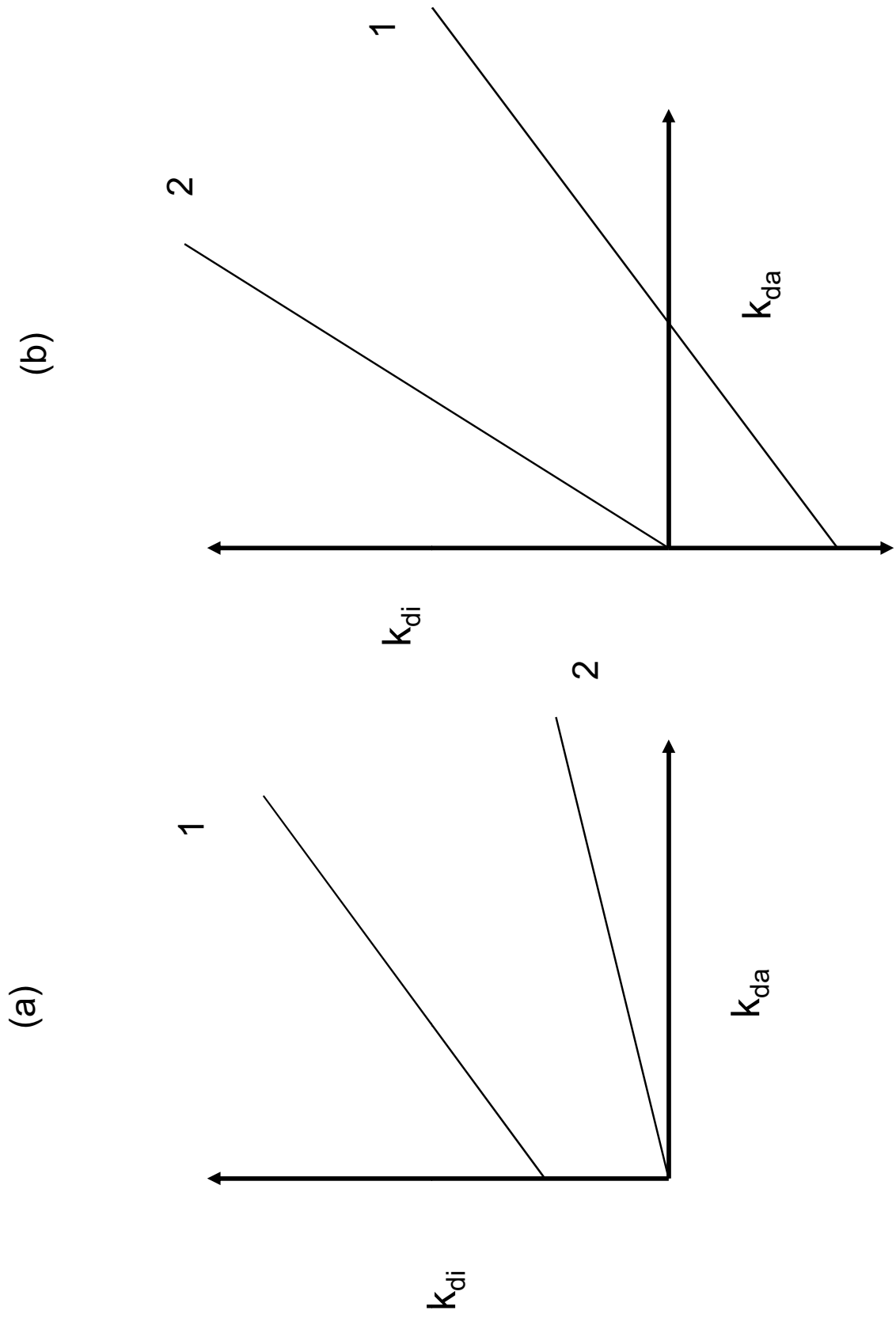


Fig. 3

Fig. 4



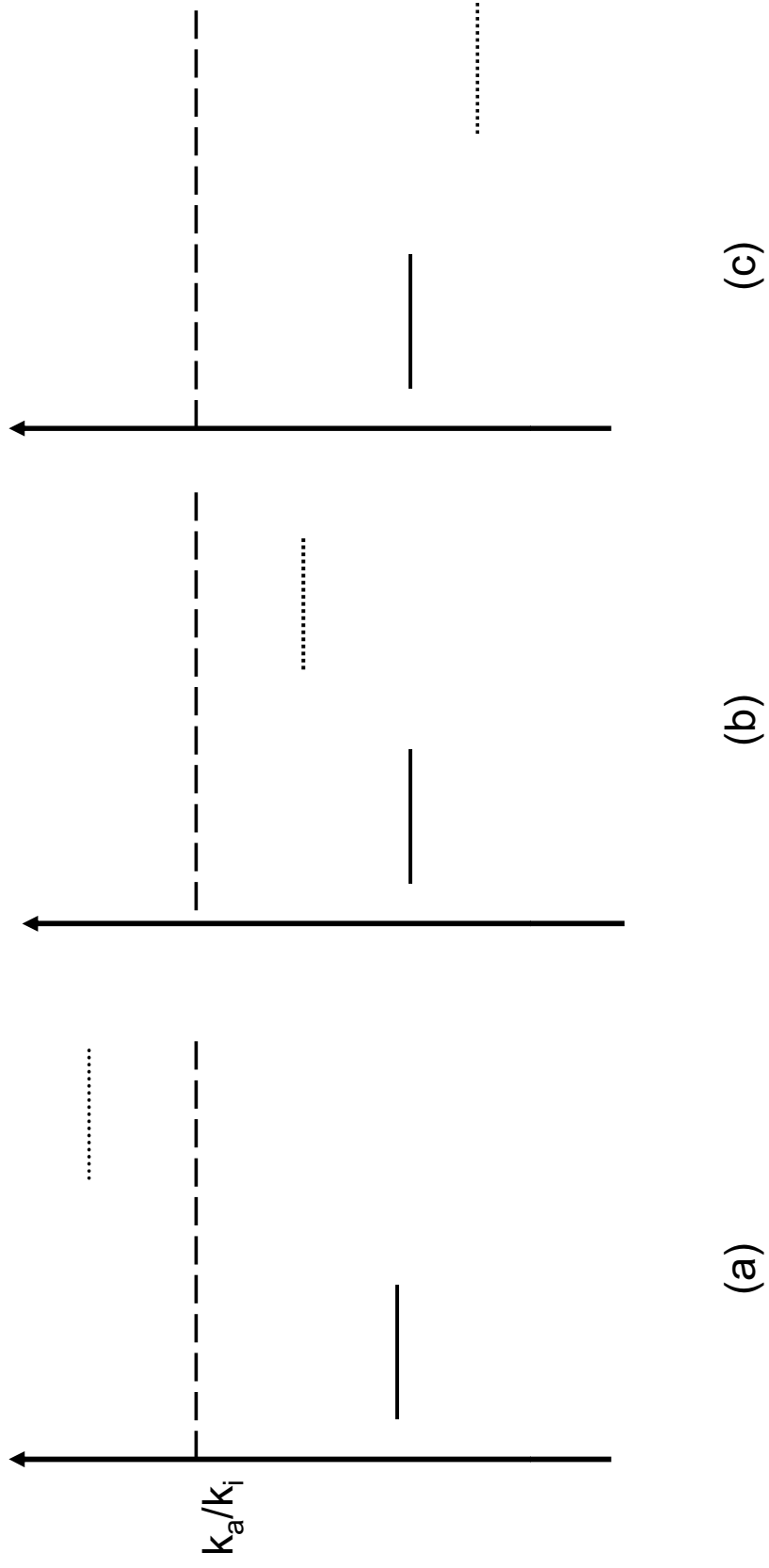


Fig. 5

Fig. 6

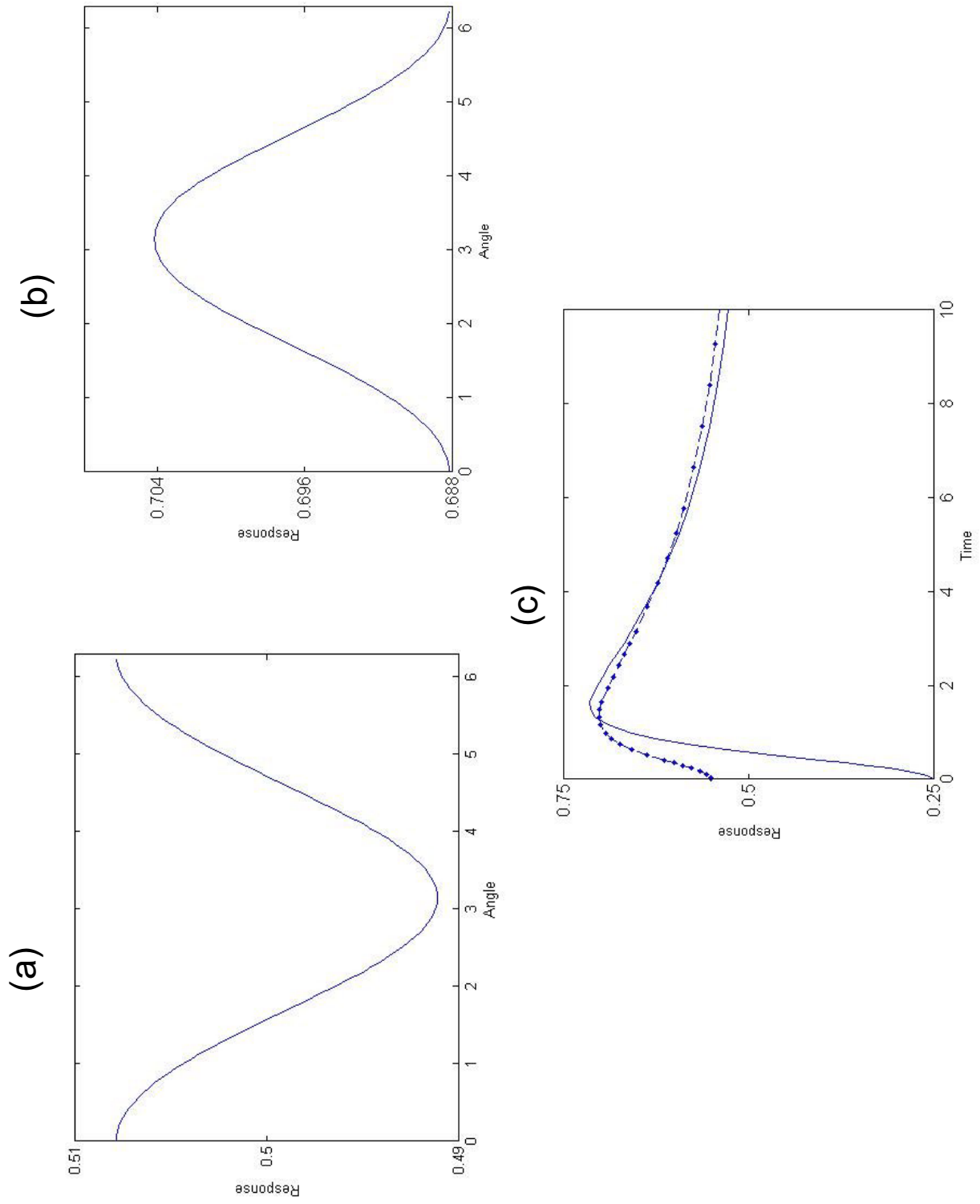


Fig. 7

