A Biochemical Filter for Frequency-based Signal Reception in Molecular Communication

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***Abstract*—Molecular Communication (MC) is a nanoscale interaction paradigm inspired by the natural ability of cells in biology to communicate through the processing, exchange, and transduction of information by biochemical reactions of molecules. The design and modeling of MC systems is the first step towards future applications based on the engineering of communication systems in biology. In this paper, a bandpass filter based on a specific type of biochemical reactions in cell communication, namely, signaling kinase cascade, is proposed for an MC receiver in a diffusion-based MC scenario. In particular, under the commonly accepted weak activation assumption, these biochemical reactions can be analytically modeled through linear systems theory. The characterization of the proposed filter, and the corresponding numerical results, demonstrate its passband properties, and its suitability for extracting signals in different frequency bands coming from different molecular transmitters.**

***Index Terms*—Biochemical filter design, molecular communication, diffusion-based channel, signal transduction network, signaling kinase cascade, nanonetworks.**

I. Introduction

The field of Molecular Communication (MC) hinges on the need to create communication systems and networks for the interconnection of autonomous nanoscale devices, or nanomachines [1]. Among other envisioned technologies, MC is directly inspired by the natural ability of cells in biology to interact with each other through the generation, propagation, and reception of molecular signals that are processed, transduced, and interpreted through biochemical processes. Such interactions enable cells' coordination and collaboration in uni- and multi-cellular organisms, and participate in most of the major cellular functionalities such as cell growth, proliferation and apoptosis [2].

The study and modeling of MC from an engineering standpoint, along with the tools from synthetic biology available today to directly control the behavior of cells and their biochemical processes, will spur the development of applications based on nanomachines directly derived from engineered cells, and their interactions. Such developments should markedly impact many fields, including medicine (e.g., developing biocompatible diagnosis and treatment systems), industry (e.g., biologically-controlled food production), and agriculture (e.g., monitoring and control of soil microbiology).

In our research, we propose the design of filters to be implemented in nanomachines and able to process signals in the biochemical domain, without the need of a conversion from the molecular domain to another domain, e.g., electrical. In our previous work [3], we proposed a notch, or bandstop, filter designed to suppress biochemical signals that oscillate around a certain frequency. In this paper, based on the diffusion-based MC model introduced in [4], [5], we propose a biochemical bandpass filter at the molecular receiver that is able to distinguish molecular signals propagated from different molecular transmitters on the basis of their frequency components.

The proposed filter is based on the biochemical mechanism employed by the cells in signal transduction networks, which realizes the reception of messages carried by molecules present in the surrounding environment to then stimulate specific cellular responses [6]. This particular biochemical mechanism involves cascades of chemical reactions, or signaling kinase cascades, between different proteins that are biological molecules synthesized by cells according to the genetic information contained in their DNA. The choice of exploiting signal transduction networks for our filter is motivated by the much shorter time-scale that characterizes their dynamics if compared to other intracellular biochemical signaling systems, such as transcription networks [6]. Moreover, as detailed in Sec. III, signaling kinase cascades can be investigated through linear systems theory under the condition of being weakly activated. In contrast to our previous work [3], where a notch filter was realized by exploiting crosstalk interactions in signal transduction pathways, in this paper we propose to implement a feedback mechanism within a signaling kinase cascade to obtain the aforementioned bandpass behavior for the reception of molecular signals with different frequency components.

The rest of the paper is organized as follows. In Sec. II the MC scenario is described, along with the main model that characterizes this MC system. Sec. III describes the analytical model of the proposed biochemical filter, while Sec. IV contains the analysis of the filter in terms of its passband properties. In Sec. V some numerical results for these properties are presented according to typical biochemical parameters. Finally, Sec. VI concludes the paper.

II. MC Scenario and System Model

We consider a communication scenario composed of two molecular transmitters and one molecular receiver, as shown

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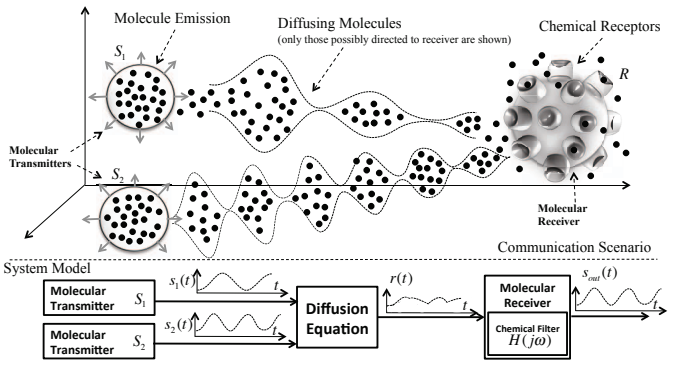

Fig. 1. Pictorial representation of the molecular communication scenario and the corresponding system model scheme.

in Fig. 1, immersed in a fluidic medium where molecules are solely subject to free diffusion in a 3-dimensional space with infinite extent across the three dimensions. Each molecular transmitter, S_k, $k \in 1, 2$, is at the three-dimensional location $\overline{x}_k$, at a distance $d_k = \|\overline{x}_k - \overline{x}_R\|$ from the receiver, where $\overline{x}_R$ is the receiver location.

A **Molecular Transmitter** sends information to the molecular receiver through an emission of molecules that results in a local change of the molecule concentration [5], denoted by the transmitted signal $s_k(t), k \in 1, 2$. The transmitted molecules are assumed of the same species and the transmitter sizes are negligible compared to the distance between each transmitter and the receiver. We consider the case where the transmitted signal $s_k(t)$ is an oscillation modulated in amplitude by a lowpass signal, namely

$$s_k(t) = P_k + \gamma_k(t) \sin(\omega_k t), \tag{1}$$

where P_k is a constant molecular concentration that keeps positive the concentration of molecules in space, $\gamma_k(t) < P_k, \forall t \geq 0$, and $\gamma_k(t)$ is a lowpass signal of bandwidth W, according to the definition in [7], where $W \ll \omega_k$. As a consequence, the transmitted signal $s_k(t)$ shows a nearly-oscillatory behavior, which corresponds to a sinusoidal variation in the local molecule concentration with frequency ω_k. We assume that the two transmitters emit molecules by modulating oscillations with different frequencies $\omega_1 < \omega_2$, where the difference between the two frequencies is much greater than the double of the lowpass signal bandwidth, namely, $\omega_2 - \omega_1 \gg 2W$. As a consequence, the bandwidths of the transmitted signals $s_1(t)$ and $s_2(t)$ do not overlap with each other, and they are separable through appropriate frequency-based filtering. There are several reasons supporting nearly-oscillatory emission of molecules, such as in (1), from a biological perspective. As an example, genes are expressed by slow reaction rates involving considerable fluctuations in cytoplasmic protein production rates [8]. Another scenario where an oscillatory behaviour is observed regards the relationship between cyclic AMP production and rate of Ca^{2+} influx into a cell [9]. This interaction establishes a negative-feedback loop able to sustain oscillations of both cAMP and Ca^{2+}.

The propagation of the transmitted signal $s_k(t), k \in 1, 2$, as shown in Fig. 1, is realized through the **Diffusion Equation** [10], [11]. Owing to the linearity of the diffusion channel, as proved in [5], the received signal $r(t)$ is the superposition of each convolution between the transmitted signal $s_k(t)$ from the kth transmitter and the Green's function of the diffusion equation [12]:

$$r(t) = s_1(t) * g_d(d_1, t) + s_2(t) * g_d(d_2, t), \tag{2}$$

where $g_d(d_k, t)$ is the Green's function defined as

$$g_d(d_k, t) = \frac{1}{(4\pi D t)^{\frac{3}{2}}} e^{-\frac{d_k^2}{4Dt}} u(t). \tag{3}$$

In (3), $u(t)$ is the step signal [7] and D is the diffusion coefficient in [cm^2 sec^{-1}], here considered constant in time and homogeneous in space, as defined in [5]. In the frequency domain [7], the received signal $R(j\omega)$ can be computed through the Fourier transform [7] of (2) as

$$R(j\omega) = S_1(j\omega) G_d(d_1, \omega) + S_2(j\omega) G_d(d_2, \omega), \tag{4}$$

where $G_d(d_k, \omega)$ is the Fourier transform of the Green's function [12]:

$$G_d(d_k, \omega) = \frac{1}{4\pi D d_k} e^{-(1-j)\sqrt{\frac{\omega}{2D}} d_k}. \tag{5}$$

ω is here intended as the frequency of a Fourier component (signal spectrum) of a time varying molecule concentration at distance d_k from the molecule emission.

The **Molecular Receiver**, as illustrated in Fig. 1, is provided with chemical receptors for reading the propagated signal $r(t)$ in terms of molecule concentration at the receiver location. This is achieved through the ligand-receptor binding reaction with the incoming molecules that compose the signal $r(t)$, as detailed in Sec. III. Our objective is to explore the possibility of developing a chemical filter embedded in the receiver, denoted in the frequency domain as $H(j\omega)$, able to interact with the received signal $R(j\omega)$ in the molecular domain and obtain an output signal $S_{out}(j\omega)$ as follows:

$$S_{out}(j\omega) = H(j\omega) R(j\omega), \tag{6}$$

where $S_{out}(j\omega)$ is as close as possible to $S_2(j\omega)$ so as to isolate $S_2(j\omega)$ from $R(j\omega)$. This implies that the filter $H(j\omega)$ should have a band of at least W around the frequency value ω_2, while minimizing the frequency components outside this band. In other words, *given a set of chemical reaction rates*, defined in Sec. III, *we seek to analytically characterize $H(j\omega)$ as a bandpass linear filter with center frequency $\omega_m = \omega_2$, and 3 dB bandwidth equal to W*. The center frequency ω_m is defined as the frequency ω where the magnitude $|H(j\omega)|$ is maximum,

$$\omega_m = \arg\max_{\omega} |H(j\omega)| = \omega_2, \tag{7}$$

while the 3 dB bandwidth is defined as the absolute difference between the center frequency ω_m and ω_{3dB}

$$|\omega_m - \omega_{3dB}| = W. \tag{8}$$

ω_{3dB} is the frequency where the magnitude $|H(j\omega)|$ is $1/\sqrt{2}$ times the max value. In other words, ω_{3dB} is the solution of the following equation:

$$|H(j\omega_{3dB})| = \frac{1}{\sqrt{2}} \max_{\omega} |H(j\omega)|. \tag{9}$$

III. Biochemical Filter Model

In this section, we detail the analytical model of a biochemical filter based on the ligand-binding process, which enables the receiver to transduce a propagated signal in terms of molecule concentration at the receiver location into a concentration of receptors bound to received molecules, followed by an m-stage signaling kinase cascade. As we mathematically prove in the following, we can design a Linear Time-Invariant (LTI) bandpass filter with the following frequency response:

$$\begin{aligned} H(j\omega) &= \left[\prod_{i=0}^{m-1} \frac{k_i}{j\omega + k_i^-}\right] \cdot \\ &\cdot \frac{k_m\left(j\omega + k_{m+1}^-\right)}{(k_{m+1}^- + k_m^-)j\omega - \omega^2 + k_{m+1}^- \cdot k_m^- + k_f \cdot k_{m+1}}, \end{aligned} \tag{10}$$

where k_i, $i = 0, 1, \ldots, m$, is the pseudo-first order phosphorylation rate at stage i, k_i^-, $i = 0, 1, \ldots, m+1$, is the dephosphorylation rate at stage i, and k_f is the feedback constant rate of the $m+1$-th stage on the m-th stage, as detailed next.

A very important signaling pathway falling in the category investigated in this paper is the epinephrine cascade [13]. The pathway is activated by the binding of epinephrine molecules to receptors molecules, called β-adrenergic, located on the surfaces of cells typically found in muscles, adipose tissues and liver. These receptors then react with molecules, called $G_{s\alpha}$, that, in the presence of adenylyl cyclase (AC) molecules, stimulate the synthesis of several cyclic adenosine monophosphate (cAMP) molecules, which activate the subsequent signaling kinase cascade. In a series of four cascaded stages, cAMP molecules activate protein kinase A (PKA) molecules, which, in turn, activate phosphorylase b kinase molecules. The latter activates glycogen phosphorylase α molecules, which, in the presence of glycogen, stimulate the production of glucose 1-phosphate molecules. After many steps, glucose 1-phosphate is converted into glucose, which is diffused into the blood.

The first part of our analytical model takes into account the ligand-receptor binding process where the molecules that compose the received signal $r(t)$ bind to receptors located at the receiver, therefore activating the subsequent signaling kinase cascade. With reference to the aforementioned epinephrine cascade, the interaction between a receptor and an incoming molecule brings a conformational change that modifies the activity of the receptor by producing $G_{s\alpha}$ molecules in the cell. This type of process is described by the following differential equation:

$$\frac{dA_0(t)}{dt} = k_0^+ r(t) A_{0f}(t) - k_0^- A_0(t), \tag{11}$$

where $A_{0f}(t)$ is the concentration of unbound receptors, $A_0(t)$ is the concentration of receptors bound to ligands (incoming molecules), and k_0^+, k_0^- are the receptor-ligand binding reaction rates. Assuming a total concentration of chemical receptors $A_{tot} = A_0 + A_{0f}$, the previous equation can be rewritten as:

$$\frac{dA_0}{dt} = k_0^+ A_{tot} r(t) \left(1 - \frac{A_0}{A_{tot}}\right) - k_0^- A_0. \tag{12}$$

Let $k_0 = k_0^+ A_{tot}$ be the pseudo-first order rate constant. Although (12) shows in general a non-linear behavior of the chemical reaction, it can be approximated by a linear differential equation in scenarios where saturation effects are negligible [14], [15]. This corresponds to the following assumptions: i) the total receptor concentration A_{tot} is constant, ii) the total concentration of chemical receptors is much higher than the concentration of bound receptors, i.e., $A_{tot} \gg A_0$, which corresponds to the assumption of weak activation of the chemical reaction [16]. As a consequence, (12) can be linearized as follows:

$$\frac{dA_0}{dt} = k_0 r(t) - k_0^- A_0. \tag{13}$$

Using frequency analysis [7], the relationship between the spectra of the received signal $R(j\omega)$ and the first kinase in the cascade, equal to the number of bound receptors $A_0(j\omega)$, can be written as:

$$A_0(j\omega) = \frac{k_0}{j\omega + k_0^-} R(j\omega) = H_0(j\omega) R(j\omega). \tag{14}$$

A common characteristic of a signaling kinase cascade is the presence, at each stage in the cascade, of an input protein species A_{i-1}, the kinase, an inactive (nonphosphorylated) protein species $\widehat{A}_i$, and an active protein species A_i. The kinase A_{i-1} activates the phosphorylation of A_i with rate k_i^+, while A_i undergoes dephosphorylation with rate k_i^-. Phosphorylation is the chemical process through which a protein, stimulated by a protein kinase, acquires a phosphate group, therefore changing its "state" from low-energy to high-energy. Dephosphorylation is the opposite process where a phosphorylated protein loses the phosphate group. When in the high-energy state, a protein becomes the protein kinase for the next stage of the cascade.

The differential equation governing the stage i of the cascade, with $i \in \{1, \ldots, m\}$, can be written as follows:

$$\frac{dA_i(t)}{dt} = k_i^+ A_{i-1}(t) \widehat{A}_i(t) - k_i^- A_i(t), \tag{15}$$

where $A_i(t)$ denotes the concentration of protein species A_i at time t, $A_{i-1}(t)$ is the concentration of the kinase phosphorylating A_i, and $\widehat{A}_i(t)$ denotes the concentration of the nonphosphorylated (inactive) protein at stage i. Upon defining the total concentration of inactive and active protein at stage i, $A_i^T = A_i + \widehat{A}_i$, (15) can be rewritten as:

$$\frac{dA_i(t)}{dt} = k_i^+ A_{i-1}(t) \left(A_i^T(t) - A_i(t)\right) - k_i^- A_i(t). \tag{16}$$

By factoring $A_i^T(t)$, we get

$$\frac{dA_i}{dt} = k_i A_{i-1} \left(1 - \frac{A_i}{A_i^T}\right) - k_i^- A_i, \tag{17}$$

where, in line with [16], we defined $k_i = k_i^+ A_i^T$ as the pseudo-first order phosphorylation rate at stage i.

In order to solve for A_i in (17), we assume that the pathway is weakly activated [16], that means $A_i \ll A_i^T$. With this assumption, which is typical of scenarios where saturation effects are negligible [14], [15], (17) simplifies to the following linear differential equation:

$$\frac{dA_i}{dt} = k_i A_{i-1} - k_i^- A_i. \tag{18}$$

By applying frequency analysis techniques to (18), we get

$$A_i(j\omega) = \frac{k_i}{j\omega + k_i^-} A_{i-1}(j\omega). \tag{19}$$

With this setup, each stage in the cascade can be analyzed as a linear time-invariant system with frequency response $H_i(j\omega)$ given by

$$H_i(j\omega) = \frac{A_i(j\omega)}{A_{i-1}(j\omega)} = \frac{k_i}{j\omega + k_i^-} = \frac{k_i}{k_i^-} \frac{1}{j\frac{\omega}{k_i^-} + 1}. \tag{20}$$

The overall frequency response of the pathway cascade including the ligand-receptor binding process in the case where A_{tot} is constant is given by

$$H(j\omega) = \prod_{i=0}^{m} H_i(j\omega) = \prod_{i=0}^{m} \frac{k_i}{k_i^-} \frac{1}{\frac{j\omega}{k_i^-} + 1}, \tag{21}$$

where $H_0(j\omega)$ is expressed in (14).

The goal of this work is the description of a pathway able to create a bandpass filter, denoted by a center frequency ω_m and a 3 dB bandwidth, as defined in (7) and (8). By design, the frequency behavior of the pathway described so far is clearly lowpass, as can be easily inferred from (21). In order to create a bandpass behavior, analyzed in Sec. IV, we propose to modify the pathway by introducing a new stage where a new protein species A_{m+1} is phosphorylated by the kinase A_m, and, on its turn, acts on A_m through a feedback with constant rate k_f, with a similar mechanism as suggested in [17]. The biochemical interaction between these two kinases is described by the following set of differential equations:

$$\begin{array}{rcl} \frac{d}{dt}A_m & = & k_m A_{m-1} - k_m^- A_m - k_f \cdot A_{m+1} \\ \frac{d}{dt}A_{m+1} & = & k_{m+1} A_m - k_{m+1}^- A_{m+1} \end{array} \tag{22}$$

Using frequency analysis [7], the second differential equation results into

$$A_{m+1}(j\omega) = \frac{k_{m+1}}{j\omega + k_{m+1}^-} A_m(j\omega), \tag{23}$$

while the first yields

$$\begin{aligned} \left(j\omega + k_m^-\right) A_m(j\omega) =& k_m A_{m-1}(j\omega) \\ & - k_f \cdot A_{m+1}(j\omega). \end{aligned} \tag{24}$$

Upon replacing (23) into (24), we get:

$$\begin{aligned} \left[j\omega + k_m^-\right] A_m(j\omega) =& k_m A_{m-1}(j\omega) \\ & - k_f \cdot \frac{k_{m+1}}{j\omega + k_{m+1}^-} A_m(j\omega). \end{aligned} \tag{25}$$

Solving for $A_m(j\omega)$, we get

$$\left[j\omega + k_m^- + k_f \frac{k_{m+1}}{j\omega + k_{m+1}^-}\right] A_m(j\omega) = k_m A_{m-1}(j\omega), \tag{26}$$

$$A_m(j\omega) = \frac{k_m \left(j\omega + k_{m+1}^-\right) A_{m-1}(j\omega)}{(k_{m+1}^- + k_m^-)j\omega - \omega^2 + k_{m+1}^- \cdot k_m^- + k_f \cdot k_{m+1}}. \tag{27}$$

In terms of frequency analysis, the overall frequency response of the designed pathway is therefore given by (10). The spectrum of the output signal from the pathway as a function of the transmitted signal spectrum can be expressed as in (6).

IV. Biochemical Filter Analysis

This section addresses the analysis of the proposed filter in terms of its passband properties, namely, the center frequency ω_m and the 3 dB bandwidth, defined in (7) and (8), respectively. To simplify this analysis, we focus on a simpler pathway with one stage of phosphorylation, i.e., $m = 1$. Most of the considerations drawn in this simpler case extend to the general case as well since, in both cases, the overall bandpass behavior of the filter is determined by the parameters of the last stage of the pathway as expressed in (27).

The frequency response of the aforementioned one-stage pathway can be found from (10) upon setting $m = 1$:

$$H_1(j\omega) = \frac{1}{j\omega + k_0^-} \frac{k_0 k_1 \left(j\omega + k_2^-\right)}{(k_2^- + k_1^-)j\omega - \omega^2 + k_2^- \cdot k_1^- + k_f \cdot k_2} \tag{28}$$

In order to find the center frequency ω_m, we first derive the magnitude of (28) against ω, then we set the derivative to zero, and finally solve for ω. After lengthy calculations, we derive the following polynomial whose real roots yield the solution ω_m:

$$\begin{array}{l} \omega^2 = y \\ ay^3 + by^2 + cy + d = 0 \end{array} \tag{29}$$

where $a = 1$, $b = \frac{3}{2}(k_2^-)^2 + \frac{1}{2}\left[(k_0^-)^2 + \alpha\right]$, $c = (k_2^-)^2\left[(k_0^-)^2 + \alpha\right]$, $d = -\frac{k_0^2\beta}{2} + \frac{(k_2^-)^2}{2}\left[\beta + (k_0^-)^2\alpha\right]$, $\alpha = (k_1^-)^2 + (k_2^-)^2 - 2k_f k_2$, and $\beta = \left[k_1^- k_2^- + k_f k_2\right]^2$.

The solution we are looking for is $\omega_m = \sqrt{y_o}$ where y_o, the solution of $ay^3 + by^2 + cy + d = 0$, can be found using the well-known formula for the root of a 3rd-order polynomial [18]. Upon setting

$$\begin{array}{rcl} \Delta_1 & = & -\frac{b^3}{27a^3} + \frac{b \cdot c}{6a^2} - \frac{d}{2a} \\ \Delta_2 & = & \left(\frac{c}{3a} - \frac{b^2}{9a^2}\right)^3 \end{array} \tag{30}$$

ω_m can be found by:

$$\sqrt{\sqrt[3]{\Delta_1 + \sqrt{\Delta_1^2 + \Delta_2}} + \sqrt[3]{\Delta_1 - \sqrt{\Delta_1^2 + \Delta_2}} - \frac{b}{3a}} \tag{31}$$

The solution ω_m for the general pathway in (10) is derived in the Appendix.

The maximum amplitude of the filter at the frequency ω_m corresponds to $H_{max} = |H_1(j\omega_m)|$. We use this value in (9) to find the value of ω_{3dB}. Upon evaluating (28) in $\omega = \omega_{3dB}$,

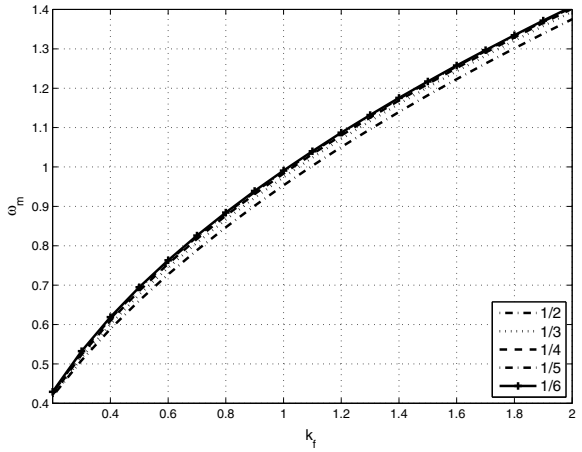

Fig. 2. Behavior of ω_m as a function of k_f. Curves are parameterized by k_0^-, shown in the legend. Other parameters are $k_0 = k_1 = k_2 = 1$, $k_0^- = k_1^-$, and $k_2^- = 0.1$.

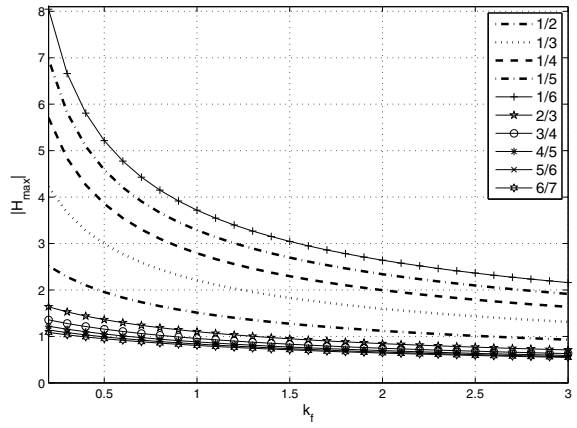

Fig. 3. Behavior of H_{max} as a function of k_f. Curves are parameterized by k_0^-, shown in the legend. Other parameters are $k_0 = k_1 = k_2 = 1$, $k_0^- = k_1^-$, and $k_2^- = 0.1$.

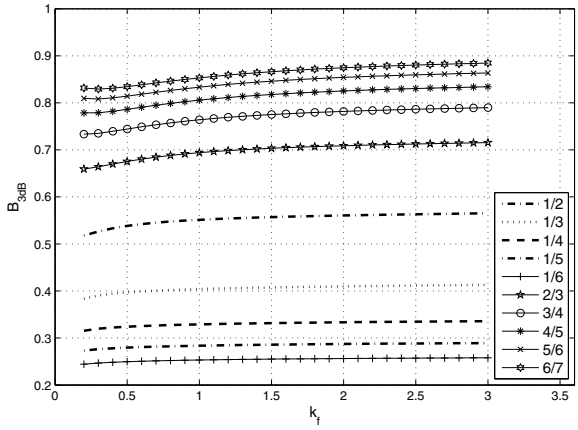

Fig. 4. Behavior of B_{3dB} as a function of k_f. Curves are parameterized by k_0^-, shown in the legend. Other parameters are $k_0 = k_1 = k_2 = 1$, $k_0^- = k_1^-$, and $k_2^- = 0.1$.

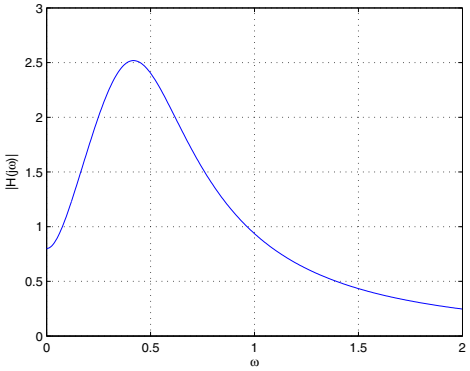

Fig. 5. Magnitude of the frequency response of filter in (28) for $k_0 = k_1 = k_2 = 1$, $k_0^- = k_1^- = 1/2$, $k_2^- = 0.1$, and $k_f = 0.2$. The peak occurs at $\omega_m = 0.4181$ while the 3dB bandwidth is $B_{3dB} = 0.5179$.

after lengthy calculations, we derive, similarly to (29), that ω_{3dB} is given by (30) and (31) with the following parameters: $a = 1$, $b = (k_0^-)^2 + \alpha$, $c = \beta + (k_0^-)^2\alpha - \gamma$, $d = (k_0^-)^2\beta - (k_2^-)^2\gamma$, $\alpha = (k_1^-)^2 + (k_2^-)^2 - 2k_f k_2$, $\beta = \left[k_1^- k_2^- + k_f k_2\right]^2$, and $\gamma = 2\frac{k_0^2 k_1^2}{H_{max}^2}$.

V. Numerical Results

We discuss two sample filter design examples and derive some rules of thumb for engineering molecular pathway cascades. Design curves are shown in Figs. 2 to 4.

Given a desired center frequency ω_m of the bandpass filter, we select the feedback constant rate k_f from Fig. 2. The feedback rate k_f is then used to determine the constant rates $k_i^-, i = 0, 1$, in order to either satisfy a desired peak gain H_{max} (from Fig. 3) or a desired 3dB bandwidth (from Fig. 4). From Figs. 3-4 we infer that H_{max} and B_{3dB} are inversely related in terms of k_f. This behavior makes pathway filter design different from conventional filter design where, at an increased cost of filter complexity, it is possible to design filters attaining any given set of specifications.

The first filter design is accomplished with the following set of typical parameters [16]: $k_0 = k_1 = k_2 = 1$, $k_0^- = k_1^- = 1/2$, $k_2^- = 0.1$, and $k_f = 0.2$. The magnitude of the frequency response of designed filter is shown in Fig. 5. The second design is accomplished with the following pathway parameters: $k_0 = k_1 = k_2 = 1$, $k_0^- = k_1^- = 1/2$, $k_2^- = 0.1$, and $k_f = 1.5$. The magnitude of the frequency response is shown in Fig. 6.

The passband of the designed filter increases for increasing values of the feedback rate k_f. From (29), the peaks of the frequency responses occur at $\omega_m = 0.4181$ for the first filter and $\omega_m = 1.1821$ for the second filter. This effect is due to the complex-conjugate pair of poles whose location is affected by k_f. As a rule of thumb, the peak of the passband occurs at the frequency $\omega_m \approx \frac{1}{2}\sqrt{\left(k_{m+1}^- - k_m^-\right)^2 - 4k_f k_{m+1}}$. The 3dB bandwidth increases for increasing feedback rates k_f as well. The peak values of these bandpass filters can be higher

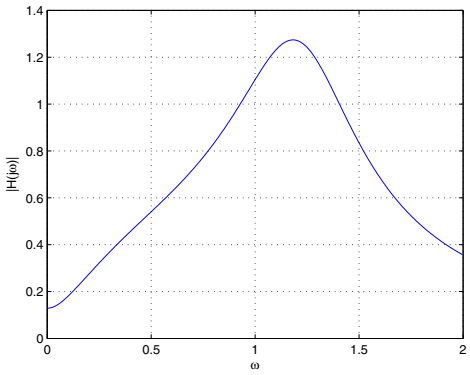

Fig. 6. Magnitude of the frequency response of filter in (28) for $k_0 = k_1 = k_2 = 1$, $k_0^- = k_1^- = 1/2$, $k_2^- = 0.1$, and $k_f = 1.5$. The peak occurs at $\omega_m = 1.1821$ while the 3dB bandwidth is $B_{3dB} = 0.5570$.

than one, thus offering the possibility to compensate for the attenuation undergone by the transmitted signals through the diffusion channel.

The proposed design, based on kinase cascade feedback loops [19] and the tuning of their parameters [20], could guide the engineering of modules that regulate cell responses [21], e.g., activation or repression of genes, according to the frequency of molecular signals, with maximum response around a desired center frequency ω_m.

VI. Conclusion

In this paper, we proposed a bandpass filter for a molecular receiver in a diffusion-based MC system for the realization of frequency-based reception of incoming signals. This filter is based on the biochemical mechanism of a signaling kinase cascade in cellular signal transduction networks, which, under the assumption of weak activation, can be analytically modeled through linear systems theory. The mathematical characterization of the proposed filter and the corresponding numerical results show that under some constraints, certain passband characteristics can be satisfied through a proper tuning of some biochemical parameters. Future work will include an analysis of the stability of such filter, and the design of a framework to facilitate its implementation in synthetic biology.

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Appendix

For the general pathway with m stages, the center frequency ω_m is found by setting to zero the derivative of the natural logarithm of $H(j\omega)$ from (10) against ω. After lengthy calculations, it results into the following polynomial:

$$\begin{aligned}&(\omega^4+\gamma\omega^2+\alpha)\left[-\textstyle\prod_{i=0}^{m-1}(\omega^2+(k_i^-)^2)+\right.\\&\left.+(\omega^2+(k_{m+1}^-)^2)\textstyle\sum_{i=0}^{m-1}\prod_{j=0,j\neq i}^{m-1}(\omega^2+(k_i^-)^2)\right]+\\&+(2\omega^2+\beta)(\omega^2+(k_{m+1}^-)^2)\textstyle\prod_{i=0}^{m-1}(\omega^2+(k_i^-)^2)=0\end{aligned} \tag{32}$$

where $\alpha = \left[k_m^- k_{m+1}^- + k_f k_{m+1}\right]^2$, $\beta = \left[k_m^- + k_{m+1}^- - 2k_m^- k_{m+1}^- + k_f k_{m+1}\right]$ and $\gamma = \left[(k_m^-)^2 + (k_{m+1}^-)^2 - 2k_f k_{m+1}\right]$ The positive real root of (32), which can be found using Matlab upon setting m, corresponds to the passband center frequency ω_m.

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