Oscillatory dynamics in the mitogen-activated protein kinase cascade

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Abstract

We have used quantitative modeling of signaling networks to show that the mitogen-activated protein kinase cascade — a highly-conserved signaling network in eukaryotes — can functions as a low-pass filter by amplifying low-frequency oscillations and attenuating high-frequency oscillations. This filtering function of the kinase cascade is in addition to other known functions such as being an ultrasensitive switch. We show how this low-pass filtering regulates downstream cellular functions and cellular physiology. We also show how the presence of scaffold proteins in the kinase cascade modifies the properties of the low-pass filter. In particular, we find that the presence of scaffold proteins destroys the properties of the low-pass filtering, and instead attenuate all oscillations. In particular, the higher the scaffold concentration, the greater the attenuation.

1. Introduction

The role of oscillatory dynamics in biological networks such as intracellular signaling pathways, and their consequences on cellular physiology, is an active area of research among systems biologists. In particular, the use of analytical techniques borrowed from electrical engineers, such as frequency domain analysis and stability analysis, is ubiquitous. In this poster, we describe the use of a computational systems-level model to study the oscillatory dynamics in the mitogen-activated protein kinase cascade. The mitogen-activated protein kinase cascade is highly conserved in eukaryotes and is involved in the control of stress response, high osmolarity response, growth and differentiation, etc. The existence of protein kinase oscillations may have important biophysical consequences. For example, intracellular waves of protein kinases may arise in the cytoplasm when these oscillations are coupled to protein kinase diffusion, which may in turn impact the spatiotemporal control that signaling can exert on the cell state [1].

The input or stimulus is, for example, the Ras protein belonging to the family of monomeric GTPases. It catalyzes the phosphorylation of the mitogen-activated protein kinase-kinase-kinase (MAPKKK). At the same time, there are also MAPKKK phosphatases that dephosphorylate the active MAPKKK* back into the inactive MAPKKK. This phosphorylation-dephosphorylation cycle is repeated for the next two stages of the protein kinase cascade, namely phosphorylation-dephosphorylation cycles of the mitogen-activated protein kinase-kinase (MAPKK) and the kinase (MAPK). The fully activated MAPK** is the output of kinase cascade. It in turn phosphorylates a variety of gene regulatory proteins in the nucleus.

There are several mechanisms that can generate sustained oscillations in biological networks. One of them is the existence of negative feedback interactions between components of the network, such as between the response and the stimulus of the cascade [2]. Biochemically, negative feedback from the response to the stimulus may arise as allosteric inhibitions in the latter's kinetics. Such modifications introduce higher-order nonlinearities to the dynamics of the biochemical interactions. These nonlinearities may destabliize the fixed points of the dynamics and replace them with limit cycles, resulting in sustained oscillations. In this article, we assume that negative feedback exists between the active MAPK** and the stimulus (i.e., Ras) and we model this feedback as an MAPK** molecule (the inhibitor) binding onto an allosteric site of a Ras molecule. Using standard enzyme kinetics, we assume that the maximum velocity V_M of the Michaelis-Menten kinetics of the Ras enzyme on the phosphorylation of MAPKKK into MAPKKK* as

$$V'_M(t) = V_M \left[1 + \eta \sin(\omega t)\right]. \qquad (1)$$

We have introduced two new parameters, $0 \leq \eta \leq 1$ the magnitude of the negative feedback, and $\omega \geq 0$ the frequency of the oscillation. The unit for ω is $2\pi \times \text{min}^{-1}$. The parameter η is dimensionless. Our task is then to study the protein kinase oscillations as we vary the two parameters, η and ω.

2. Results

In the unsaturated cascade, approximately one-half of the kinase population is phosphorylated at steady-state. We now look at the magnitude of the oscillations (i.e., the fluctuations) when the cascade is operating in this regime as a function of the oscillation parameters η and ω. We find that, for small values of the frequency ω, the magnitude of the oscillations in the steady-state MAPK activity is greater than that in the steady-state MAPKK activity, which is in turn greater than that in the steady-state MAPKKK activity. However, this amplification of the oscillations disappers at larger values of the frequency ω. For a particular value of the amplitude η, we consider the ratio of the total power of the steady-state MAPK activity to the total power of the steady-state MAPKKK activity. We call this ratio or gain, ρ, and study it as a function of the stimulus frequency ω. The total power is simply the integral with respect to time of the activity. In Fig. 1, the power gain ρ is plotted. The horizontal dashed line denotes $\rho = 1$, i.e., where oscillations in the steady-state MAPK activity has the same magnitude as the oscillations in the steady-state MAPKKK activity. For $\omega < 10^0$ approximately, the oscillations in the steady-state MAPK activity are amplified, whereas for $\omega > 10^0$, the oscillations are attenuated. Thus, oscillations with periods longer than approximately 6 min. are amplified, whereas oscillations with shorter periods are attenuated. The power gain vs. frequency curve for the unsaturated cascade has the characteristics of a low-pass filter.

We next show whether scaffold proteins indeed attenuate oscillations, as first proposed by Kholodenko [1]. We look at how the kinase oscillations are attenuated, if any, by the presence of scaffold proteins. First, we look at the mean steady-state MAPK activity, which is depicted in the inset of Fig. 2. It is seen that the steady-state activity can be amplified by up to approximately 20% when there are as many scaffolds as there are kinases. However, the further increase of scaffolds causes the steady-state activity to eventually decrease. We next measure the magnitude of the oscillations (normalized by their mean steady-state activity) as a function of scaffold concentration, and observed that the oscillations are indeed attenuated as the scaffold concentration increases. This is shown in Fig. 2.

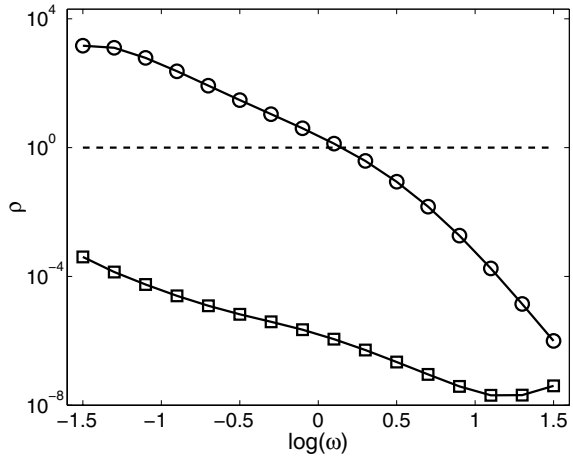

Figure 1. Ratio ρ of the total power of the steady-state MAPK activity to the total power of the steady-state MAPKKK activity as a function of the stimulus frequency ω. The circle symbols denote values for the unsaturated cascade. The square symbols denote values for the saturated cascade.

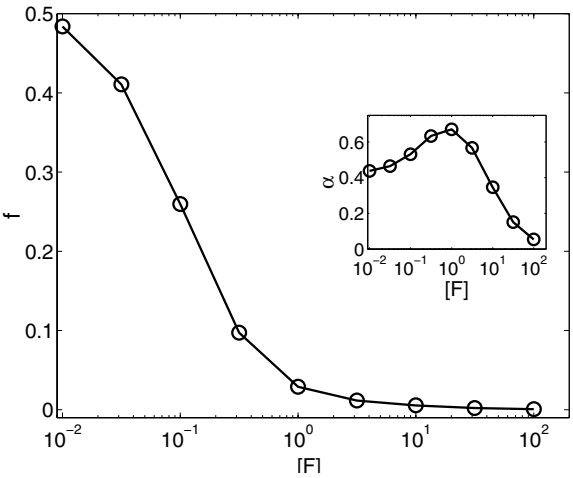

Figure 2. Increasing scaffold protein concentration $[F]$ reduces magnitude f of kinase oscillations.

References

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