*These problems are based on the work of Uri Alon.*

**Problem UA.1** (The BIG model and dynamical compensation)**.**
Prof. Alon called his model for glucose regulation as the "BIG" model, referring to beta cells, insulin, and glucose. The glucose regulation circuit is shown below.

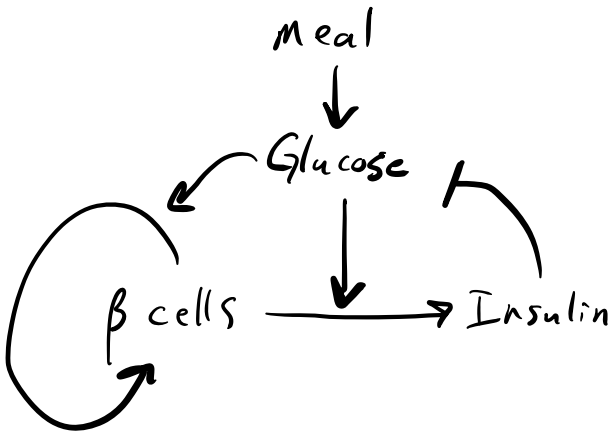


Figure 1: A sketch of the BIG model.

He argued that circuits like this, where a molecular species promotes both cell proliferation and excretion, are motifs in systems medicine.

He modeled the circuit with the following differential equations.

$$\frac{\mathrm{d}B}{\mathrm{d}t} = (p(G) - r(G))B, \tag{UA.1}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = q\,B f(G) - \gamma\, I, \tag{UA.2}$$

$$\frac{\mathrm{d}G}{\mathrm{d}t} = m - s\,I\,G. \tag{UA.3}$$

Here, proliferation and death of beta cells is dependent on glucose; glucose is needed to fuel proliferation, but glucotoxicity can lead to cell death. Insulin is produced with a rate $qB$, enhanced by glucose. Finally, glucose is injected by eating a meal $m$, but is regulated by insulin. The parameter $s$ is referred to as **insulin sensitivity**; the greater the insulin sensitivity, the more effectively glucose is removed.

The BIG model exhibits an interesting property as it pertains to robustness. Imagine that a patient is sitting at a steady state glucose, beta cell, and insulin level with an insulin sensitivity $s_1$. Suddenly, the patient's insulin sensitivity changes to $s_2$. The patient eats a meal, and the dynamics of the glucose concentration will be exactly the same as if the patient had an insulin sensitivity of $s_1$. That is, the dynamics of glucose are completely independent of the insulin sensitivity. The same is true for the parameter $q$.

Prof. Alon refers to this independence as **dynamical compensation**. It is a special kind of robustness. Exact adaptation, which we talked about in lecture, is a feature of systems with dynamical compensation, but dynamical compensation goes further. The *dynamics* of a variable are independent, in this case, of $s$ and $q$, and this is true for any parameter values, provided a steady state exists.

To demonstrate that this circuit exhibits dynamical compensation with respect to glucose, we need to show that $\mathrm{d}G/\mathrm{d}t$ is independent of $s$ and $q$ and further that the initial conditions are independent of $s$ and $q$.

a) Assuming that the initial conditions are a steady state, show that the BIG model exhibits dynamical compensation with respect to glucose. *Hint:* Try defining new variables $\hat{B} = qsB$ and $\hat{I} = sI$.

b) Do the dynamics of insulin and beta cells also exhibit dynamical compensation with respect to $s$ and $q$?

**Problem UA.2** (Fibroblast bistability)**.**
During his lectures, Prof. Alon discussed a simple model for fibroblasts, in which fibroblasts secrete platelet-derived growth factor (PDGF) which enhances their own growth in what he termed an "autocrine loop." A sketch of the circuit is below.

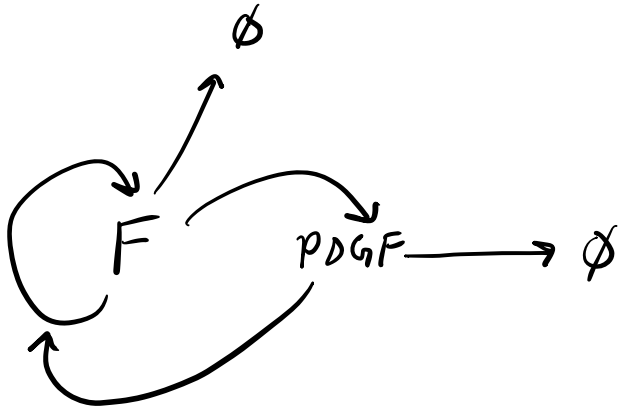


Figure 2: A sketch of a simple fibroblast regulation circuit.

a) Explain why the following system of ODEs is reasonable for modeling this system.

$$\frac{\mathrm{d}c_{\mathrm{F}}}{\mathrm{d}t} = aF - e_{\mathrm{F}}Fc_{\mathrm{F}} - \gamma_{\mathrm{F}}c_{\mathrm{F}}, \tag{UA.4}$$

$$\frac{\mathrm{d}F}{\mathrm{d}t} = p_{\mathrm{F}}c_{\mathrm{F}}\left(1 - \frac{F}{K}\right)F - d_{\mathrm{F}}F. \tag{UA.5}$$

Here, $c_{\mathrm{F}}$ is the concentration of PDGF, and the parameter $K$ is referred to as the **carrying capacity** of fibroblast cells. Be sure to explain what each term represents.

b) Nondimensionalize these ODEs to give

$$g_{\mathrm{F}}^{-1}\frac{\mathrm{d}c_{\mathrm{F}}}{\mathrm{d}t} = \alpha F - \varepsilon F c_{\mathrm{F}} - c_{\mathrm{F}}, \tag{UA.6}$$

$$\frac{\mathrm{d}F}{\mathrm{d}t} = c_{\mathrm{F}}\left(1-F\right)F - F, \tag{UA.7}$$

where all variables are dimensionless and $g_{\mathrm{F}}$, $\varepsilon$, and $\alpha$ are dimensionless parameters.

c) In his lecture, Prof. Alon made the approximation that the PDGF concentration could be taken to be at steady state, that is that $\mathrm{d}c_{\mathrm{F}}/\mathrm{d}t \approx 0$. Why is this a reasonable approximation?

d) Employ the approximation that $\mathrm{d}c_{\mathrm{F}}/\mathrm{d}t \approx 0$ and derive expressions for the fixed points (steady state fibroblast concentration) of this system. What is the condition for bistability? Comment on what this means physically and with respect to the patient being stricken with fibrosis.

**Problem UA.3** (Fibroblast bistability with macrophages)**.**
Building on the previous problem we will consider the second model Prof. Alon presented for fibroblasts when in the presence of macrophages, which enter a tissue as part of an immune response. In this model, the PDGF secreted by the fibroblasts serves to enhance proliferation of macrophages. The macrophages also secrete a growth factor that enhances proliferation of fibroblasts. A sketch of the circuit is shown below.

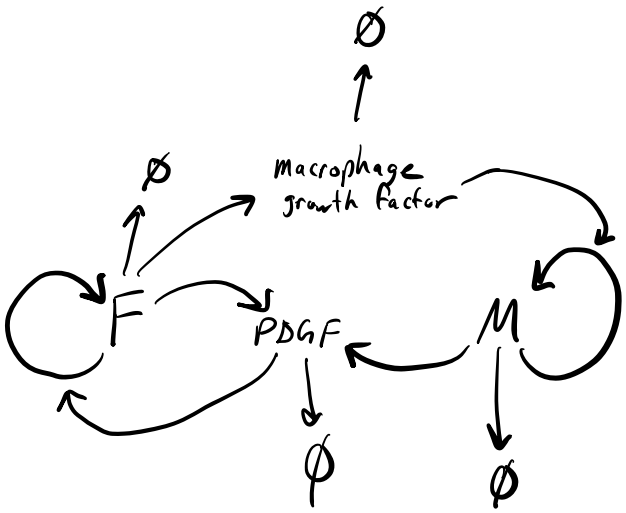


Figure 3: A sketch of a fibroblast regulation circuit in the presense of macrophages.

Prof. Alon graphically showed the results of adding the macrophages. Here, we will explicitly update the dynamical equations and analyze them. Denoting by $c_{\mathrm{M}}$ the concentration of growth factor that is secreted by fibroblasts that is specific to macrophages and be $M$ the concentration of macrophages, we have

$$\frac{\mathrm{d}c_{\mathrm{F}}}{\mathrm{d}t} = aF + b_{\mathrm{F}}M - e_{\mathrm{F}}Fc_{\mathrm{F}} - \gamma_{\mathrm{F}}c_{\mathrm{F}}, \tag{UA.8}$$

$$\frac{\mathrm{d}c_{\mathrm{M}}}{\mathrm{d}t} = b_{\mathrm{M}}F - e_{\mathrm{M}}Mc_{\mathrm{M}} - \gamma_{\mathrm{M}}c_{\mathrm{M}}, \tag{UA.9}$$

$$\frac{\mathrm{d}F}{\mathrm{d}t} = p_{\mathrm{F}}c_{\mathrm{F}}\left(1 - \frac{F}{K}\right)F - d_{\mathrm{F}}F, \tag{UA.10}$$

$$\frac{\mathrm{d}M}{\mathrm{d}t} = p_{\mathrm{M}}c_{\mathrm{M}}M - d_{\mathrm{M}}M. \tag{UA.11}$$

a) The above equations have the same form as in the previous problem, except for the dynamics in the number of macrophages, $M$. What assumption about the macrophage carrying capacity was made?

b) Nondimensionalize the dynamical equations to give

$$g_{\mathrm{F}}^{-1}\frac{\mathrm{d}c_{\mathrm{F}}}{\mathrm{d}t} = \alpha F + \beta_{\mathrm{F}}M - \varepsilon Fc_{\mathrm{F}} - c_{\mathrm{F}}, \tag{UA.12}$$

$$g_{\mathrm{M}}^{-1}\frac{\mathrm{d}c_{\mathrm{M}}}{\mathrm{d}t} = \beta_{\mathrm{M}}F - Mc_{\mathrm{M}} - c_{\mathrm{M}}, \tag{UA.13}$$

$$\frac{\mathrm{d}F}{\mathrm{d}t} = c_{\mathrm{F}}\left(1 - F\right)F - F, \tag{UA.14}$$

$$d^{-1}\frac{\mathrm{d}M}{\mathrm{d}t} = c_{\mathrm{M}}M - M, \tag{UA.15}$$

where all variables are dimensionless, as are the parameters.

c) Again assume $\mathrm{d}c_{\mathrm{F}}/\mathrm{d}t \approx 0$ and $\mathrm{d}c_{\mathrm{M}}/\mathrm{d}t \approx 0$ and write down two dimensionless differential equations for the dynamics of $F$ and $M$.

d) Show that $M = F = 0$ is a fixed point, regardless of the parameter values.

e) It can be shown that there are either one, two, or three fixed points with $M = 0$. (In fact, you may have shown this in the previous problem.) It can be further shown that there are either zero, one, or two fixed points with $M > 0$. Instead of proving these facts analytically, we will instead plot nullclines and look for crossings. To that end, make a dashboard that displays the two nullclines with sliders to manipulate the relevant parameters. Comment on the fixed points that you encounter and what they represent physiologically.

f) What should be true of the parameter values to avoid fibrosis?