

Connectivity and Control Equations

Elasticity Coefficients

The control coefficients, C_E^J and C_E^S measure the response of a system variable, such as a flux or species concentrations to a change in an enzyme activity or concentration. These coefficients only make sense in the intact pathway and cannot be measured on isolated enzymes.

To complement the system dependent control coefficients, the theory also introduces a local measure called the elasticity, ε . The elasticity measures the rate response of an isolated reaction step to changes in its immediate environment. Thus, an enzyme that catalyzes a single substrate/product reaction will have at least three elasticities, an elasticity with respect to the substrate, product and enzyme activity, thus:

$$\varepsilon_S^v, \varepsilon_P^v, \text{ and } \varepsilon_E^v$$

Elasticities are described by the relation:

$$\varepsilon_S^v = \frac{\partial v}{\partial S} \frac{S}{v} = \frac{\partial \ln v}{\partial \ln S}$$

where v is the local reaction rate of an isolated step and S the concentration of any molecular species or parameter that might affect the reaction rate. Note that the definition uses partial derivatives to emphasize that the concentrations and values of the participating factors other than the referenced one are held constant. This means for example that if we measure the elasticity of a reaction with respect to its substrate then the concentration of product and enzyme must be held constant.

The elasticity is a measure of how sensitive a reaction rate is to changes in its immediate environment, in addition the sensitivity is scaled to remove any measuring units so that the elasticity is also a dimensionless quantity.

Elasticities can be easily computed algebraically if we know the rate law, for example we can compute the elasticity for a simple mass-action rate in the following way:

$$\text{If } v = kS$$

then

$$\frac{\partial v}{\partial S} = k$$

Scaling the derivative by v and S gives

$$\varepsilon_S^v = \frac{kS}{kS} = 1$$

If we take another example, say a second-order reaction, $v = kS^2$, the elasticity can be shown to have a value of 2. In general, a mass-action reaction of the form:

$$v = kS^n$$

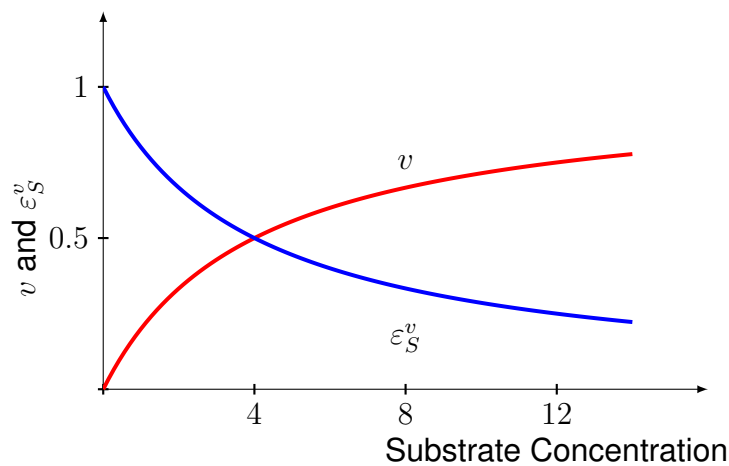
will have an elasticity of:

$$\varepsilon_S^v = n$$

These simple exercises show us that the elasticity can be interpreted as the kinetic order of the reaction. For simple mass-action kinetics the elasticity is a constant, however for enzyme catalyzed reaction the elasticity will vary according to the substrate concentration. For example, the substrate elasticity of a simple irreversible Michaelis-Menten rate law can be shown to be:

$$v = \frac{V_{\max} S}{K_m + S}$$
$$\varepsilon_S^v = \frac{K_m}{K_m + S}$$

We can plot the substrate elasticity and the reaction rate together:



Note that the elasticity starts at a value one, that is a kinetic order of one and decreases to zero as the enzyme approaches saturation, i.e a kinetic order of zero. If the reaction is reversible, the elasticities are not limited to a maximum value of unity but can far exceed this depending on how close the reaction is to equilibrium. In addition, product elasticities will be **negative** since they decrease a rate when increased. Likewise, elasticities for activators will be **positive** and elasticities for inhibitors will be **negative**.

Elasticities: Summary

Elasticities are defined by:

$$\varepsilon_S^v = \frac{\partial v}{\partial S} \frac{S}{v} = \frac{\partial \ln v}{\partial \ln S} \approx \frac{v\%}{S\%}$$

Elasticities are related to kinetics orders. They are usually positive for substrates and negative for products.

Elasticities are dimensionless.

The special elasticity, ε_E^v equals unity if the reaction rate is proportional to the enzyme concentrations.

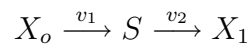
$$\varepsilon_E^v = 1$$

Connectivity Theorem

The connectivity theorem is probably the most important result in the theory of cellular networks. The theorem relates the control coefficients to the elasticities, that is it relates system wide properties to local properties:

$$\sum_{i=1}^n C_{E_i}^J \varepsilon_S^{v_i} = 0$$

Together with the summation theorems, the connectivity theorem allows one to write control coefficients entirely in terms of elasticities. For example, a two step pathway such as:



There is one connectivity theorem for every species in a pathway so that in the above example there will only be one connectivity theorem centered around S :

$$C_{E_1}^J \varepsilon_S^{v_1} + C_{E_2}^J \varepsilon_S^{v_2} = 0$$

In addition, there will be a flux summation theorem:

$$C_{E_1}^J + C_{E_2}^J = 1$$

These two equations can be combined to give expressions that relate the control coefficients in terms of the elasticities, thus:

$$C_{E_1}^J = \frac{\varepsilon_S^2}{\varepsilon_S^2 - \varepsilon_S^1}$$

$$C_{E_2}^J = -\frac{\varepsilon_S^1}{\varepsilon_S^2 - \varepsilon_S^1}$$

These equations, possibly the most important result of the theory, allow us to understand how system responses depend on local properties.

Using these equations we can look at some simple extreme behaviors. For example, let us assume that the first step is completely insensitive to its product, S, then $\varepsilon_S^1 = 0$. In this case, the control coefficients reduce to:

$$C_{v_1}^J = 1$$

$$C_{v_2}^J = 0$$

That is all the control (or sensitivity) is on the first step. This situation represents the classic rate-limiting step that is frequently mentioned in text books. The flux through the pathway is completely dependent on the first step. Under these conditions, no other step in the pathway can affect the flux. The effect is however dependent on the complete insensitivity of the first step to its product. Such a situation is likely to be rare in real pathways. In fact the classic rate limiting step has almost never been observed experimentally. Instead, a range of "limitingness" is observed, with some steps having more "limitingness" (control) than others. We can shift control off the first step by increasing the product inhibition.

Advanced Topics

By a slight rearrangement, we can use an elasticity to predict the change in reaction rate given a change in substrate or product using the relation:

$$\frac{\delta v}{v} = \varepsilon_S^v \frac{\delta S}{S}$$

In fact, so long as the changes are small, we can predict the change in reaction rate when a number of factors change, for example, the change in reaction rate when the substrate, product and say an activator, A, change, then the overall change in rate is simply the sum of the changes:

$$\frac{\delta v}{v} = \varepsilon_S^v \frac{\delta S}{S} + \varepsilon_P^v \frac{\delta P}{P} + \varepsilon_A^v \frac{\delta A}{A}$$

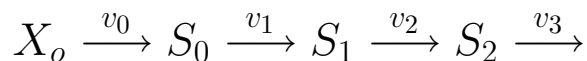
In general, if an enzyme is perturbed in n ways, then the net change in rate is given by the **local response equation**:

$$\frac{\delta v}{v} = \sum_{i=1}^n \varepsilon_{x_i}^v \frac{\delta x_i}{x_i}$$

Derivation of Connectivity Theorem

The control coefficients give us information about the system, while elasticities tell us something about the local environment of a particular enzyme. What relationship exists between the two?

We can discover a relationship using the following thought experiment. Consider a segment of a pathway:



where X_o is a fixed boundary species. Let us increase the activity of reaction v_1 by increasing the concentration of E_1 by an amount δE_1 . This change will cause the pathway to evolve to a new steady state with an increase in S_1 and S_2 but a decrease in S_0 . In fact, all species upstream of the perturbation will decrease and all concentrations downstream will increase, The pathway flux, J , will also increase as a result.

Let us now decrease the activity of v_2 by decreasing the concentration of E_2 . Let us decrease E_2 by δE_2 until the pathway flux is restored to the original level, that is the overall effect on the flux due to both operations is $\delta J = 0$.

What happens to the species concentrations? Consider S_0 , we note that no parameter has been perturbed upstream of S_0 , in particular X_o is unchanged, in addition we know by design that the rate through v_0 has not changed. If X_o is unchanged and v_0 is unchanged then it must be the case the S_0 is unchanged. A similar argument can be made for S_3 so that it too is unchanged. What of S_1 ? The first perturbation increased S_1 , the second perturbation also increased S_1 , therefore on balance S_1 will have increased.

The net effect of all these changes is:

$$E_1 \Rightarrow E_1 + \delta E_1$$

$$E_2 \Rightarrow E_2 - \delta E_2$$

$$\delta J = 0$$

$$\delta S_0 = 0$$

$$\delta S_2 = 0$$

$$\delta S_1 > 0$$

We can express these changes in terms of the system response equation and the local response equation. Focusing first on v_1 we note that two changes have occurred at v_1 , E_1 and S_1 have changed, we can express this change in v_1 using the local response equation:

$$\frac{\delta v_1}{v_1} = \varepsilon_{S_1}^{v_1} \frac{\delta S_1}{S_1} + \varepsilon_{E_1}^{v_1} \frac{\delta E_1}{E_1} = 0$$

Likewise we can also write a local response equation for v_2 as:

$$\frac{\delta v_2}{v_2} = \varepsilon_{S_1}^{v_2} \frac{\delta S_1}{S_1} + \varepsilon_{E_2}^{v_2} \frac{\delta E_2}{E_2} = 0$$

In both cases, the equations must equal zero ($\delta v/v = 0$) because by design, we know that $\delta J = 0$. Finally we can write the system response equation. This will include two terms corresponding to the changes in E_1 and E_2 (no other parameter was changed), thus:

$$\frac{\delta J}{J} = C_{E_1}^J \frac{\delta E_1}{E_1} + C_{E_2}^J \frac{\delta E_2}{E_2} = 0$$

Again, the response must equation zero since by design $\delta J = 0$. Since a reaction rate is proportional to the enzyme concentrations, we know that both $\varepsilon_{E_1}^{v_1}$ and $\varepsilon_{E_2}^{v_2}$ must equal one, therefore we can re-express the local equations as:

$$\varepsilon_{S_1}^{v_1} \frac{\delta S_1}{S_1} = -\frac{\delta E_1}{E_1}$$

$$\varepsilon_{S_1}^{v_2} \frac{\delta S_1}{S_1} = -\frac{\delta E_2}{E_2}$$

We can insert these equations into the system response equation to give:

$$-\frac{\delta J}{J} = C_{E_1}^J \varepsilon_{S_1}^{v_1} \frac{\delta S_1}{S_1} + C_{E_2}^J \varepsilon_{S_1}^{v_2} \frac{\delta S_1}{S_1} = 0$$

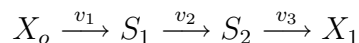
Since we know that $\delta S_1 \neq 0$, it must be the case that:

$$C_{E_1}^J \varepsilon_{S_1}^{v_1} + C_{E_2}^J \varepsilon_{S_1}^{v_2} = 0$$

This theorem, relates the control coefficients to the elasticities and for this reason is called the **connectivity theorem**. In general, for a given species, S , that interacts with n reactions, the connectivity theorem is written as:

$$\sum_{i=1}^n C_{E_i}^J \varepsilon_S^{v_i} = 0$$

For a three step pathway:



we will have two connectivity theorems centered around S_1 and S_2 and one summation theorem, again we can combine them and express the control coefficients in terms of the elasticities:

$$C_{E_1}^J = \varepsilon_1^2 \varepsilon_2^3 / D$$

$$C_{E_2}^J = -\varepsilon_1^1 \varepsilon_2^3 / D$$

$$C_{E_3}^J = \varepsilon_1^1 \varepsilon_2^2 / D$$

where

$$D = \varepsilon_1^2 \varepsilon_2^3 - \varepsilon_1^1 \varepsilon_2^3 + \varepsilon_1^1 \varepsilon_2^2$$