Glossary

Amplification

The term amplification could be used in two slightly different contexts. (1) Concentration amplification: an input signal at small concentrations controls an output signal at large concentrations. For example, an enzyme operating in uM range can regulate the amount of its product exiting in mM range. The relationship between the input and output signals can be linear or nonlinear. This denotation resembles the meaning of amplification used in electric engineering, in which an input voltage of smaller amplitude (e.g. from an MP3 player) controls, through an amplifier, an output voltage of larger amplitude (which is fed to speakers). (2) Percentage amplification: a small % change in the input signal causes a greater % change in the output signal, regardless of their concentration ranges. This second definition is compatible with the term ultrasensitivity used in this course. With ultrasensitivity, the relationship between the input and output signals is nonlinear.

Adaptation

Adaptation is the process by which a homeostatic mechanism is activated to restore the internal state of the system after initial perturbation.

Bifurcation

In a dynamic system, a bifurcation point refers to the parameter condition at which a small change made to the parameter values causes a sudden qualitative change in the system's behavior. For instance, NF-kB signaling can be either monostable or oscillatory (monostable and oscillatory are qualitatively different system behaviors) depending on the concentration of the extracellular signal such as interleukin 1 (IL-1). Bifurcation occurs at a certain concentration of IL-1, below which the NF-kB level is monostable, and above which NF-kB oscillates.

Bistability

Bistability is the capability of a system to rest in one of two discrete stable steady states under the same external condition. The two stable steady states are usually separated by an unstable steady state. Switching from one stable steady state to the other is usually triggered by some stimulatory signal, but staying in the other state does not require the signal to be persistent. Differentiation from a precursor cell type to a more differentiated cell type can be viewed as bistable switching, by which differentiated cells would remain differentiated even after the signal is no longer present in the system.

Cooperative binding

When a macromolecule has multiple binding sites for its ligand, the macromolecule exhibits cooperative binding if the binding of ligand at one site affects the affinity for the binding of ligand at another site. Positive cooperative binding occurs if initial binding increases the affinity for subsequent binding. Negative cooperative binding occurs if initial binding decreases the affinity for subsequent binding.

Covalent modification cycle

A covalent modification cycle is a reversible process in which a protein is activated (inactivated) by covalent modification (e.g. phosphorylation) and inactivated (activated) by removal of the covalent modification (e.g. dephosphorylation). Modification and de-modification are usually carried out by separate enzymes (e.g. kinase to phosphorylate and phosphatase to dephosphorylate). Zero-order ultrasensitivity occurs when one or both of the two enzymes work at saturated conditions.

Deterministic modeling/simulation

This approach models a system with a set of coupled ordinary differentiation equations (ODE) or partial differentiation equations (PDE). Starting from the same parameter conditions, each run of numerical integration of the equations generates identical time evolution of the system.

Extrinsic noise

Extrinsic noise is the variation in gene expression due to fluctuations and population variability in the factors (e.g., abundance of transcription factors, RNA polymerase, and ribosome, etc.) that influence the rate of promoter activation, transcription, translation, and degradation.

Feedback

Feedback is a process whereby some form of the output of a system is passed (fed back) to the input to control the output itself. If the feedback signal works to reinforce the output, it is a positive feedback. Conversely, if the feedback signal works to mitigate the output, it is a negative feedback.

First-order reaction

When the rate of reaction is proportional to the concentration of one reactant, the reaction is a first-order reaction. For instance, the degradation of protein usually proceeds in first order. The first-order rate constant k generally has a unit form of time^{-1}. The half-life of the reactant is ln2/k.

$$\mathrm{A} \xrightarrow{k} \mathrm{P} \qquad \frac{d[P]}{dt} = k[A]$$

Gain

See “response coefficient”

Gene expression noise

Gene expression noise refers to random fluctuations in gene expression in a single cell or variations in gene expression in a population of cells. It is often interchangeably used with the term stochasticity in gene expression. The fluctuation or variation comes from two sources: intrinsic noise and extrinsic noise.

Gillespie algorithm

Gillespie algorithm is a Monte Carlo method developed by Dan Gillespie to simulate discrete, stochastic chemical reactions. It takes random numbers, generated from exponential distributions determined by the number of molecules and reaction rate constants in the system, to decide which reaction will occur next and how soon.

Hill coefficient

See "Hill function"

Hill function

The Hill function was originally created to describe the positive cooperative binding of oxygen molecules to hemoglobin. It has a form of

$$Y = \frac{Y_{\max} X^n}{K^n + X^n},$$

where n is called Hill coefficient, and K is equal to the concentration of X that produces half of the maximal response. When the Hill coefficient is 1, the Hill equation reduces to Michaelis-Menten form. When the Hill coefficient is significantly greater than 1, the Y vs. X curve is sigmoid, indicating an ultrasensitive response. Oxygen binding to hemoglobin molecule, which has four binding sites, has a Hill coefficient of 2.8. Therefore Hill coefficient describes the steepness of a sigmoid-shaped response.

Homeostasis

Homeostasis is the capability of a biological system to maintain a relatively stable internal milieu in a fluctuating, and sometimes stressful, external environment.

Hormesis

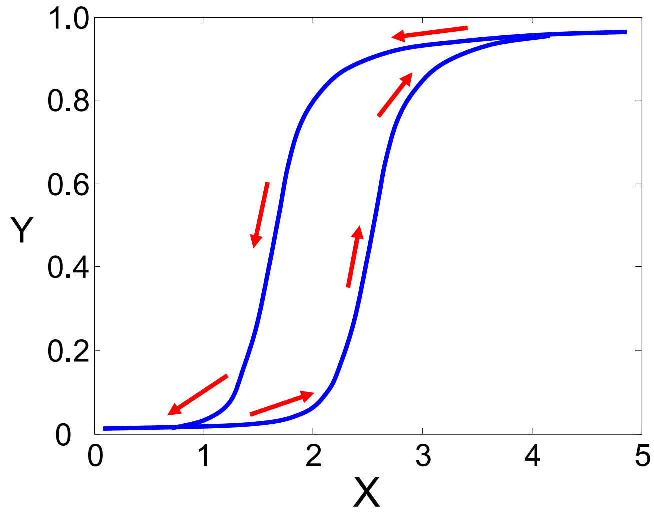
Hormesis represents a phenomenon of nonmonotonic biological dose response induced by an exogenous physical/chemical stressor. At low doses, the response either increases or decreases from the baseline level; whereas at high doses, the response changes its direction, leading to a graphically U- or inverted U-shaped curve overall.

Hyperbolic response

A hyperbolic response or rectangular hyperbola describes the shape of the dose response curve for which Michaelis-Menten kinetics are involved. See "Michaelis-Menten response" for more.

Hysteresis

Hysteresis describes a situation where the response obtained with the system starting in one state is different from that obtained with the system starting in another state. A typical example is the volume of the lung in response to air inflation and deflation. The volume of the lung follows a path on the way to inflation that is different than the path on the way to deflation. The figure below depicts a typical hysteresis type of response. Starting from a low level of Y, as the input X increases, the system generates a response curve that is different from the curve generated if the system starts from a high level of Y and X decreases. In the context of biochemical network, hysteresis is a concept closely associated with a bistable system. Hysteresis forms the basis for cellular memory and irreversibility.



Intrinsic noise

Intrinsic noise is the random fluctuation in gene expression due to the stochastic nature that is inherent to biochemical processes involved in gene expression, including promoter activation, transcription, translation, and degradation.

Michaelis-Menten response

A Michaelis-Menten response has a function of the form:

$$Y = \frac{Y_{\max} X}{K + X},$$

where Y_{max} is the maximum response at high concentrations of X, and K is equal to the concentration of X that produces half of the maximal response. The Y vs. X dose response curve has a hyperbolic shape. When X is far less than K, Y responds to X in a nearly linear manner.

Multi-step signaling

Multi-step signaling refers to a type of response motif that an input signal impinges on two sequential steps of a signaling cascade. This type of interaction has the potential to generate ultrasensitivity. A generic example is as follows: a transcription factor may induce some immediate early genes, such as cFos, and both cFos and the transcription factor are required to induce downstream target genes.

Negative feedback

Negative feedback is a process whereby some form of the output of a system is passed (fed back) to the input to mitigate the output. It is the predominant network structure to achieve homeostasis. Negative feedback also has the potential to produce oscillation.

Nullcline

For a system containing two variables (X and Y), Y nullcline is the line drawn by using all the pairs of X and Y values that satisfy dY/dt = 0 (null). X nullcline is the line drawn by using all the pairs of X and Y values that satisfy dX/dt = 0. In most cases, the Y nullcline is equivalent to the steady-state Y vs. X dose response curve, and the Y nullcline is equivalent to the steady-state X vs. Y dose response curve.

Positive feedback

Positive feedback is a process whereby some form of the output of a system is passed (fed back) to the input to reinforce the output. Positive feedback can be used to enhance sensitivity of the output in response to the input (ultrasensitivity). It is also the network structure for bistability. Double negative feedback is a special type of positive feedback.

Response motif

Response motif is a relatively simple biological circuit building block that frequently appears in complex molecular networks and possesses a specific input/output signaling (dose-response) property. In the literature, it may also be called signaling motif or network motif.

Response coefficient

If an input signal X regulates a target molecule Y, either directly or indirectly, the response coefficient refers to the ratio of the steady-state fractional change in the level of Y to the fractional change in the level of X. Mathematically it is expressed as:

$$R_X^Y = \lim_{\Delta X \to 0} \frac{\Delta Y / Y}{\Delta X / X} = \frac{dY / Y}{dX / X} = \frac{d \ln Y}{d \ln X}.$$

Since it is equivalent to the logarithmic derivative, sometimes it is also called logarithmic gain, or gain. In the literature, it is also called sensitivity of Y in response to X. When response coefficient is 1, Y has a proportional relationship with X, i.e., if X increases by 1%, Y will also increase by 1%. When response coefficient is greater than 1, if X increases by 1%, Y will increase by more than 1%. If response coefficient is significantly greater than 1, Y is said to have an ultrasensitive response to X and graphically the Y vs. S curve is sublinear. When response coefficient is smaller than 1, if X increases by 1%, Y will increase by less than 1%. If response coefficient is significantly less than 1,Y is said to have a subsensitive response to X and graphically the Y vs. S curve is superlinear.

Second-order reaction

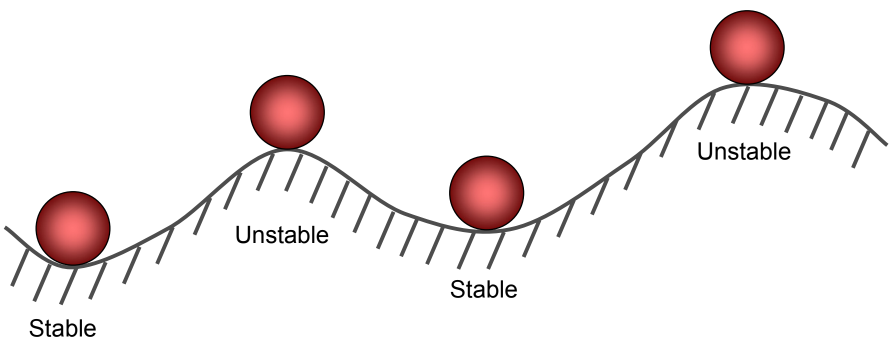
When the rate of reaction is proportional to the concentrations of two reactants or the square of one reactant, the reaction is said to be second-order. A typical example is ligand binding to a receptor. The association rate is proportional to the concentrations of both the free ligand and free receptor. However, the dissociation rate at which the ligand-receptor complex splits back into free ligand and free receptor is first-order since the rate is only proportional to the concentration of the ligand-receptor complex. Two identical protein monomers coming together to form a homodimer is also a second-rate reaction, in which the dimerization rate is proportional to the square of the concentration of the monomer. The second-order rate constant k generally has a unit form of $\text{concentration}^{-1}\text{time}^{-1}$, e.g., $M^{-1}sec^{-1}$.

$$\mathrm{A + B} \xrightarrow{k} \mathrm{P} \qquad \frac{d[P]}{dt} = k[A][B]$$

$$\mathrm{A + A} \xrightarrow{k} \mathrm{P} \qquad \frac{d[P]}{dt} = k[A]^2$$

Stable steady state

A stable steady state is a steady state to which a system tends to move back after being perturbed slightly. Stable steady states are sometimes referred to as attractor states.



Steady state

A system is said at steady state when its current state will remain unchanged over time.

Stochastic gene expression

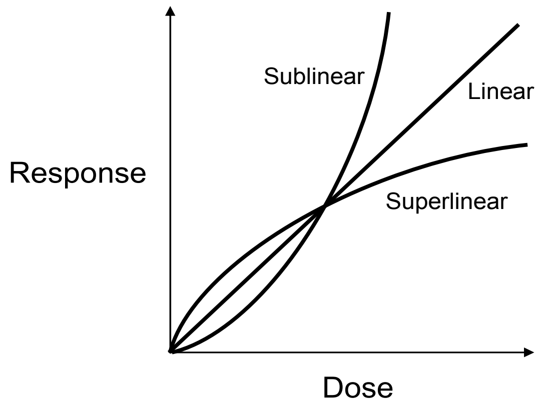
Stochastic gene expression refers to random fluctuation or variation in the abundance of a protein in a cell or among a population of cells as a result of random occurrence of promoter activation, transcription, translation, and degradation events. It is often interchangeably used with the term gene expression noise, which contains both intrinsic and extrinsic sources. But on many occasions stochastic gene expression is used to refer to intrinsic noise only.

Stochastic modeling/simulation

Chemical reactions are stochastic in nature because collisions between reacting molecules are random. The randomness can be so significant that it can not be safely ignored when a small number of molecules are involved, as in the case of gene expression at relatively low levels. With stochastic simulation, the order and timing of reactions are probabilistic and are selected by random numbers drawn from certain distributions. As a result, each run of a simulation generates different time evolution of the system even under the same parameter condition. The most commonly used stochastic algorithm is the Gillespie method, with several subsequently modified versions that speed up computation.

Sublinear

By convention, a (part of) dose response curve is sublinear if the shape of the curve is concave upward.



Superlinear

A (part of) dose response curve is superlinear if the shape of the curve is concave downward. Sometimes it is also written as supralinear. See "sublinear" for graphic illustration.

Ultrasensitivity

Generally, a dose response is ultrasensitive if the shape of the curve is significantly steeper than the hyperbolic, Michaelis-Menten form, i.e., it has a sigmoid shape on a linear scale. If the dose response curve can be approximated by a Hill function, the curve is ultrasensitive when the Hill coefficient is significantly greater than 1. More strictly speaking, ultrasensitivity refers to a dose response or part of one that has a response coefficient significantly greater than 1. In some dose range, a small percentage change in the dose causes a much greater percentage change in the response.

Unstable steady state

An unstable steady state is a steady state to which a system tends not to return after slightly perturbed away from it. See "stable steady state" for graphic illustration

Zero-order ultrasensitivity

Zero-order ultrasensitivity is an ultrasensitive response that usually occurs in association with a covalent modification cycle. In this case, one of the two enzymes is regarded as the input signal, and its modified or de-modified product is the response variable. Zero-order ultrasensitivity occurs when the protein being modified or de-modified is in excess and the modifying enzyme and or de-modifying enzyme is saturated.

Zero-order reaction

When the rate of reaction is independent of the concentrations of the reactants, the reaction is a zero order reaction. Increasing the concentrations of the reactants will not spend up the reaction, and decreasing the concentrations will not slow down the reaction. For instance, in an enzymatic reaction, if the substrate is so abundant that it completely saturates the enzyme, then the reaction proceeds in zero order. The zero-order rate constant k generally has a unit form of mol/sec or M/sec.

$$A \xrightarrow{k} P \qquad \frac{d[P]}{dt} = k$$