Bioinformatics: Network Analysis

Kinetics of Regulatory Networks: Basic Building Blocks

COMP 572 (BIOS 572 / BIOE 564) - Fall 2013
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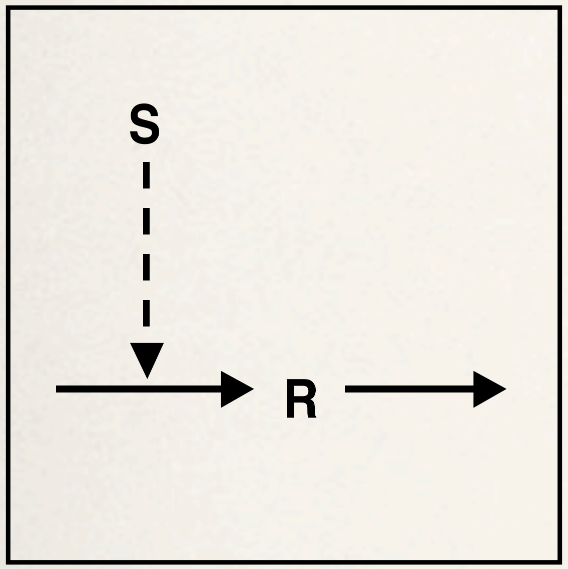
Basic Building Blocks

- Here we show how simple signaling pathways can be embedded in networks using positive and negative feedback to generate more complex behaviors - toggle switches and oscillators - which are the basic building blocks of the dynamic behavior shown by non-linear control systems.

Protein Synthesis and Degradation: Linear Response



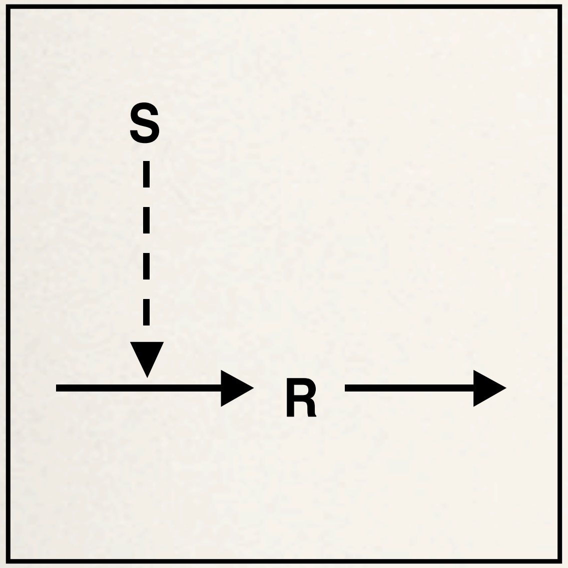
Using the law of mass action, we have:

$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R,$$

S: signal strength (concentration of mRNA)

R: response magnitude (concentration of protein)

Protein Synthesis and Degradation: Linear Response

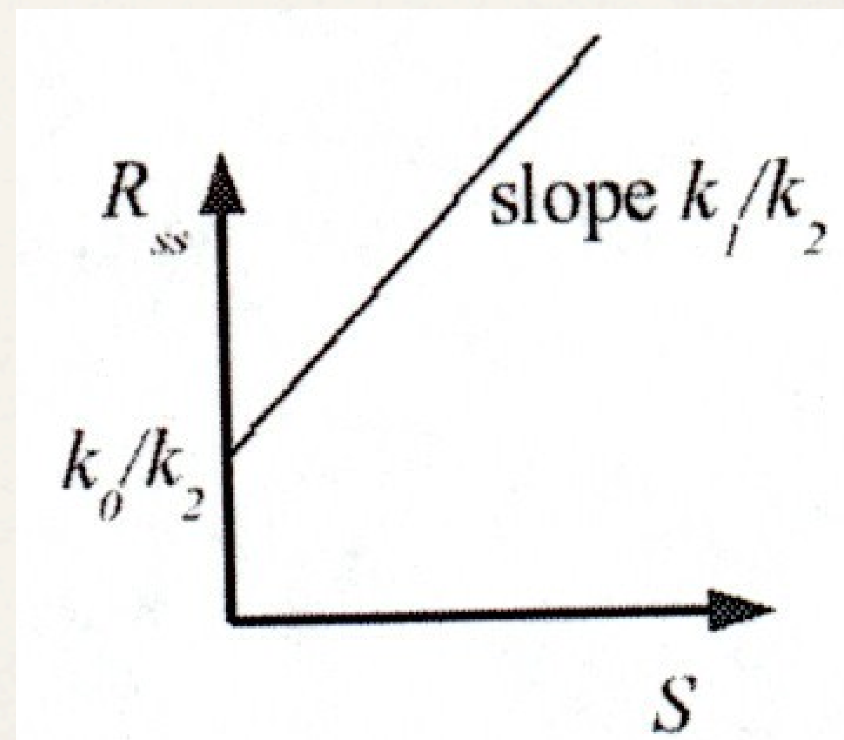


Using the law of mass action, we have:

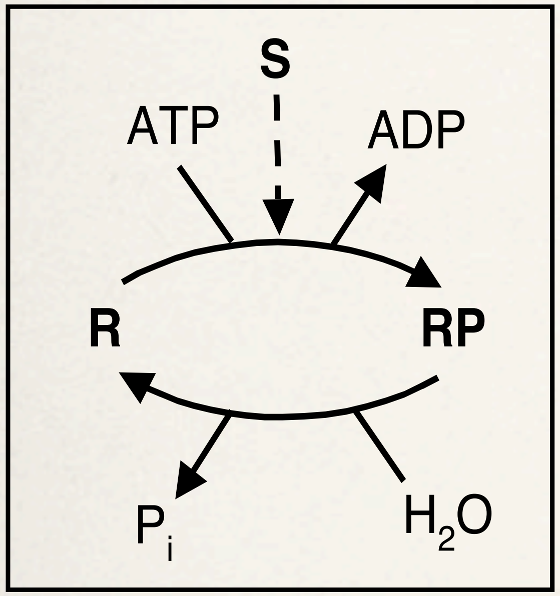
$$\frac{dR}{dt} = k_0 + k_1 S - k_2 R,$$

Steady-state solution:

$$R_{ss} = \frac{k_0 + k_1 S}{k_2}$$



Phosphorylation and Dephosphorylation: Hyperbolic Response



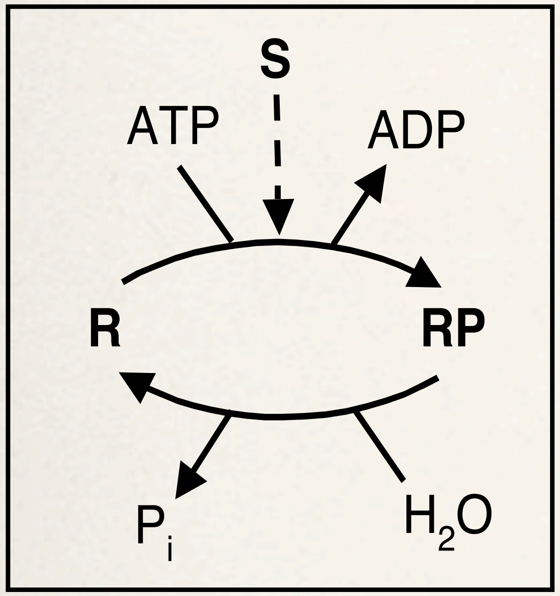
Using the law of mass action, we have:

$$\frac{dR_P}{dt} = k_1 S(R_T - R_P) - k_2 R_P.$$

R_P: concentration of the phosphorylated form of the response element

R_T: total concentration of the response element

Phosphorylation and Dephosphorylation: Hyperbolic Response



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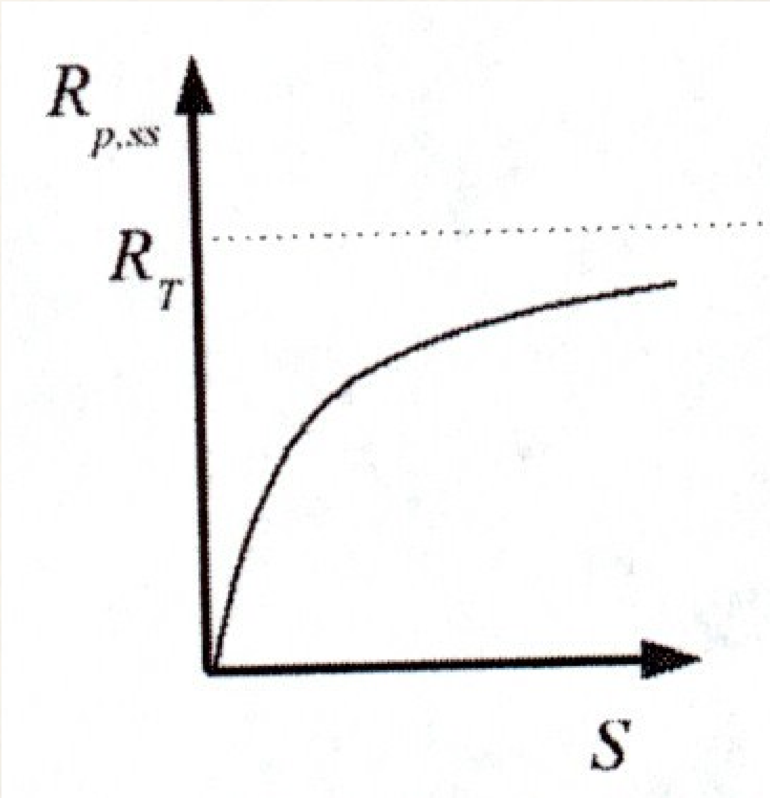
$$\frac{dR_P}{dt} = k_1 S(R_T - R_P) - k_2 R_P.$$

Steady-state solution:

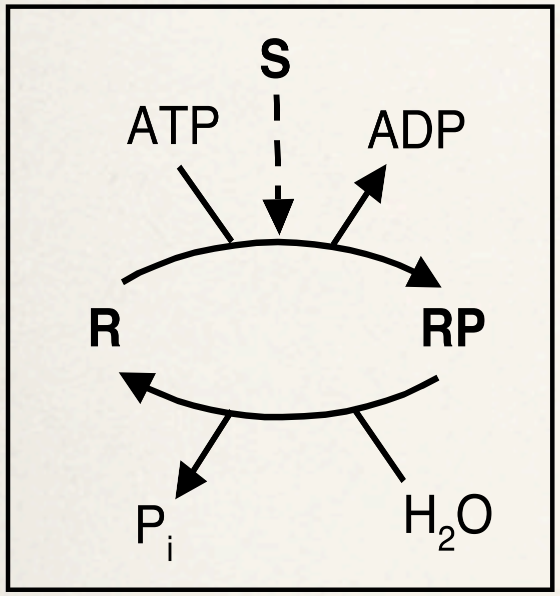
$$R_{P,ss} = \frac{R_T S}{(k_2/k_1) + S}$$



Linear and Hyperpolic Responses

- Linear and hyperbolic curves share the properties of being graded and reversible:
  - Graded means that the response increases continuously with signal strength. A slightly stronger signal gives a slightly stronger response.
  - Reversible means that if the signal strength is changed from $S_{initial}$ to S_{final}, the response at S_{final} is the same whether the signal is being increased ($S_{initial}>S_{final}$) or decreased ($S_{initial}>S_{final}$).

Phosphorylation and Dephosphorylation: Buzzer



Assuming Michaelis-Menten kinetics:

$$\frac{dR_P}{dt} = \frac{k_1 S(R_T - R_P)}{K_{m1} + R_T - R_P} - \frac{k_2 R_P}{k_{m2} + R_P}$$

Steady-state is a solution of the equation:

$$k_1 S(R_T - R_P)(K_{m2} + R_P) = k_2 R_P (K_{m1} + R_T - R_P).$$

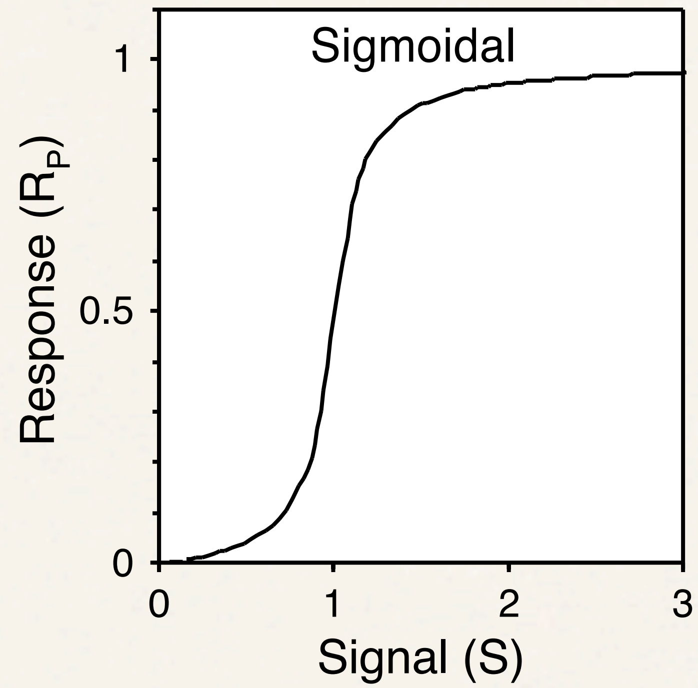
The biophysically acceptable solution ($0<R_P<R_T$) of this equation is:

$$\frac{R_{P,ss}}{R_T} = G(k_1, S, k_2, \frac{K_{m1}}{R_T}, \frac{K_{m2}}{R_T}),$$

where the Goldbeter-Koshland function, G, is defined as:

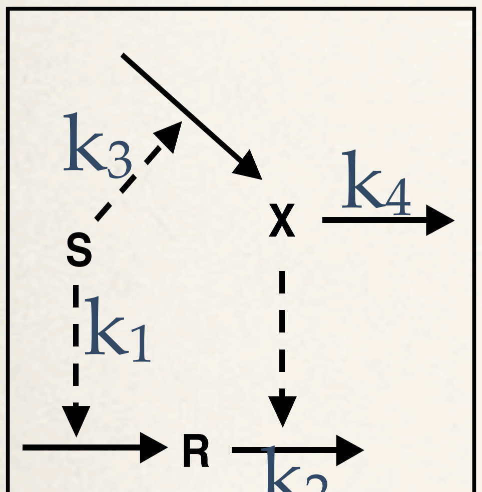
$$G(u, v, J, K) = \frac{2uK}{v - u + vJ + uK + \sqrt{(v - u + vJ + uK)^2 - 4(v - u)uK}}.$$

Phosphorylation and Dephosphorylation: Buzzer



A sigmoidal response is continuous and reversible, but abrupt. The element behaves like a buzzer, where one must push hard enough on the button to activate the response. In terms of phosphorylation, the signal S must be strong enough to create a noticeable change of the equilibrium.

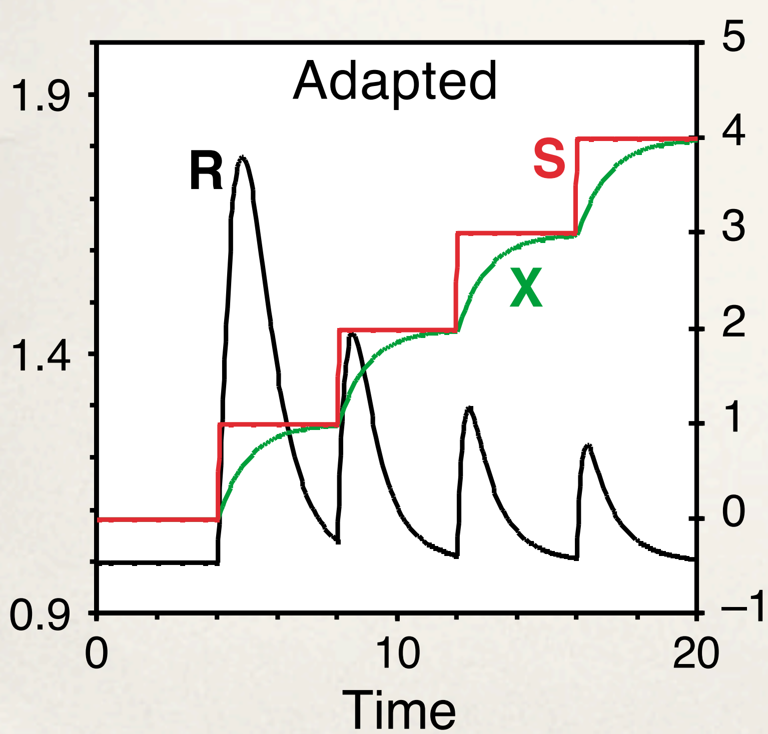
Perfect Adaptation: Sniffer



feed-forward

$$\frac{dR}{dt} = k_1 S - k_2 X \cdot R \qquad R_{ss} = \frac{k_1 k_4}{k_2 k_3}$$

$$\frac{dX}{dt} = k_3 S - k_4 X \qquad X_{ss} = \frac{k_3 S}{k_4}$$

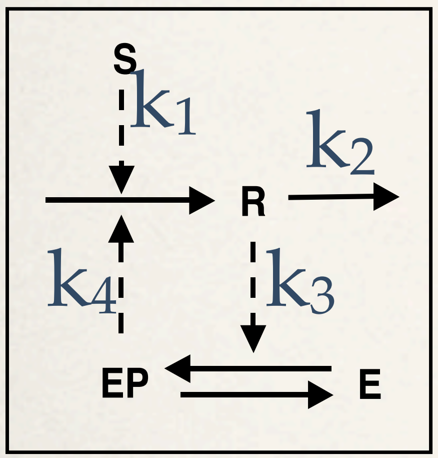


The response mechanism exhibits perfect adaptation to the signal. Although the signaling pathway responds transiently to changes in signal strength, its steady-state response R_{SS} is independent of S and is only controlled by the ratio of the four kinetic rates of the system.

Such behavior is typical of chemotactic systems, which respond to an abrupt change in attractants or repellents, but then adapt to a constant level of the signal.

Our own sense of smell operates this way; hence, this element is termed a <u>sniffer</u>.

Positive Feedback: One-way Switch

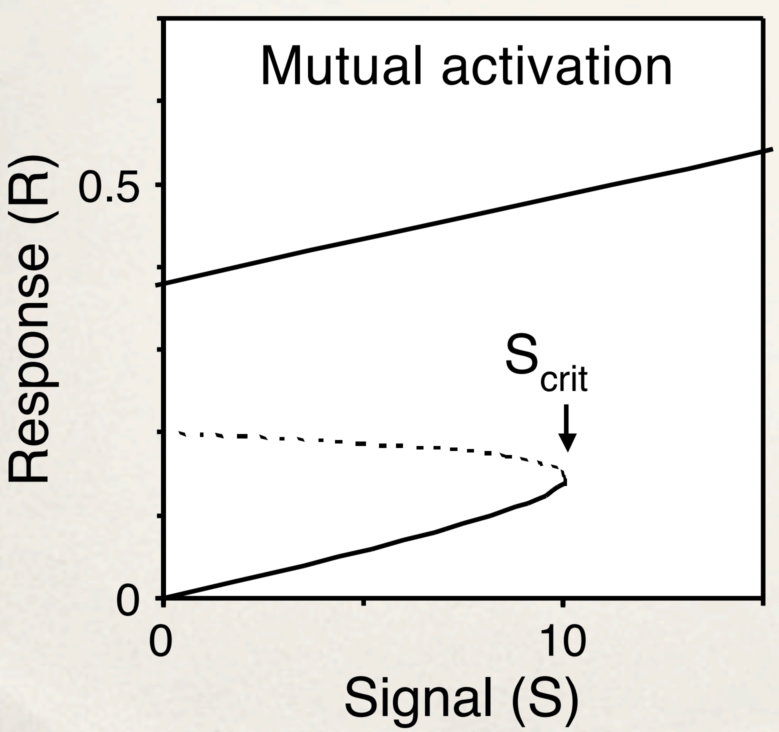


feedback

R activates enzyme E (by phosphorylation), and EP enhances the synthesis of R:

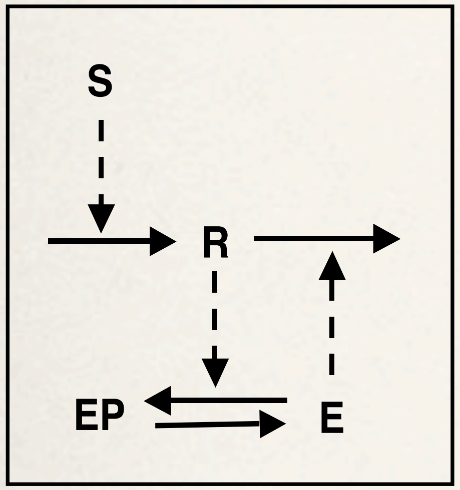
$$\frac{dR}{dt} = k_4 E_P(R) + k_1 S - k_2 R.$$

a Goldbeter-Koshland function



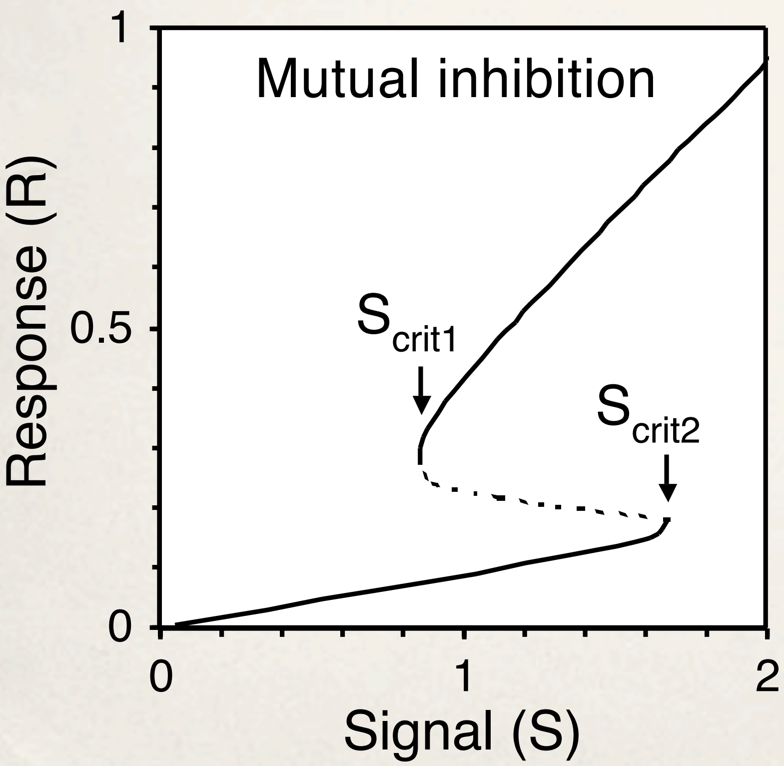
In the response curve, the control system is found to be bistable between 0 and S_{crit}. In this regime, there are two stable steady-state response values (on the upper and lower branches, the solid lines). The is called a one-parameter bifurcation. Which value is taken depends on the history of the system. After the signal threshold S_{crit} has been crossed once, the system will remain on the upper curve. This is termed a one-way switch. Apoptosis is an example for this behavior, where the decision to shut down the cell must be clearly a one-way switch.

Mutual Inhibition: Toggle Switch



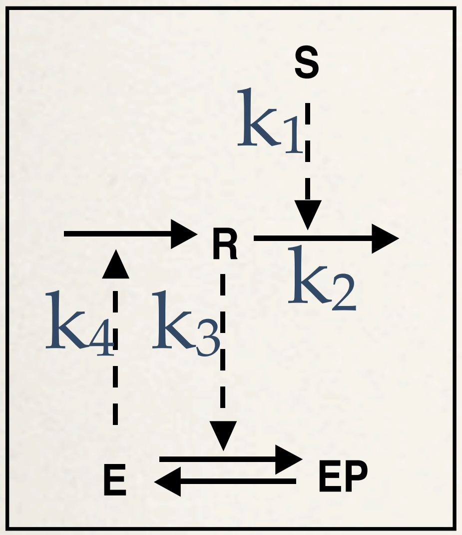
The same as the previous case, with the only difference that E now stimulates degradation of R.

$$\frac{dR}{dt} = k_o + k_1 S - k_2 R - k_2' E(R) \cdot R$$
$$E(R) = G(k_3, k_4 R, J_3, J_4)$$



This systems leads to a discontinuous behavior. This type of bifurcation is called a toggle-switch. If S is decreased enough after starting from a high level, the switch will go back to the off-state on the lower curve meaning a small response R. For intermediate stimulus strength (S_{crit1}<S<S_{crit2}), the response of the system can be either small or large, depending on the history of S(t). This is often called hysteresis. Biological examples of such behavior include the lac operon in bacteria.

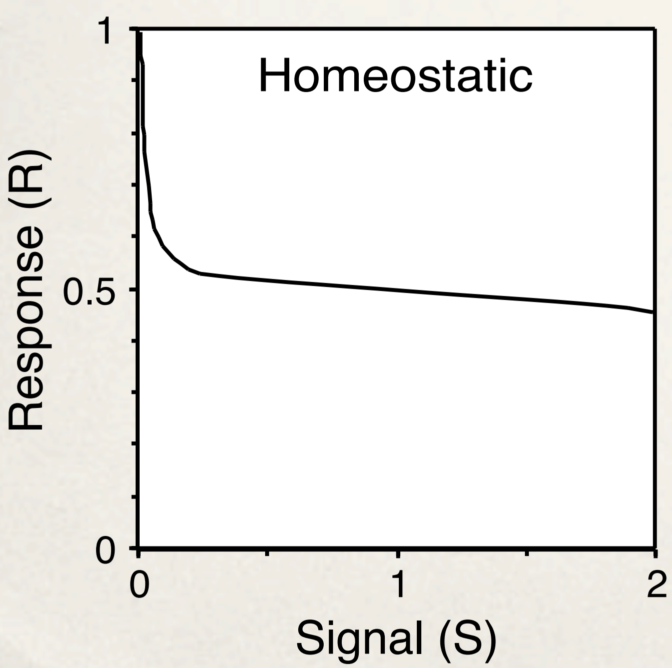
Negative Feedback: Homeostasis



The response element, R, inhibits the enzyme E catalyzing its synthesis.

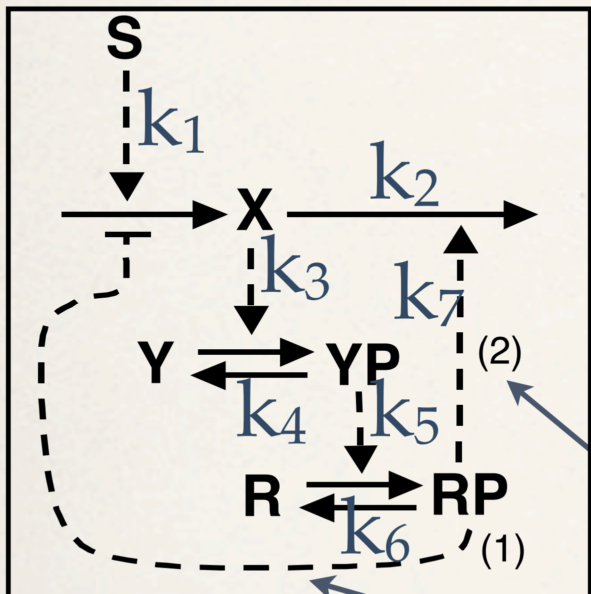
$$\frac{dR}{dt} = k_4 E(R) - k_2 S \cdot R$$

$$E(R) = G(k_4, k_3 R, J_3, J_4).$$



This type of regulation is called <u>homeostasis</u>. It is sort of an adaptation, but not a sniffer, because stepwise increases in S do not generate transient changes in R.

Negative Feedback: Oscillation



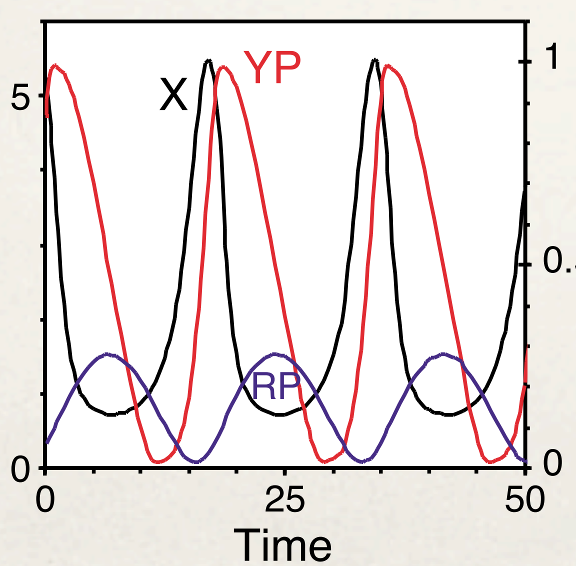
Second scenario:

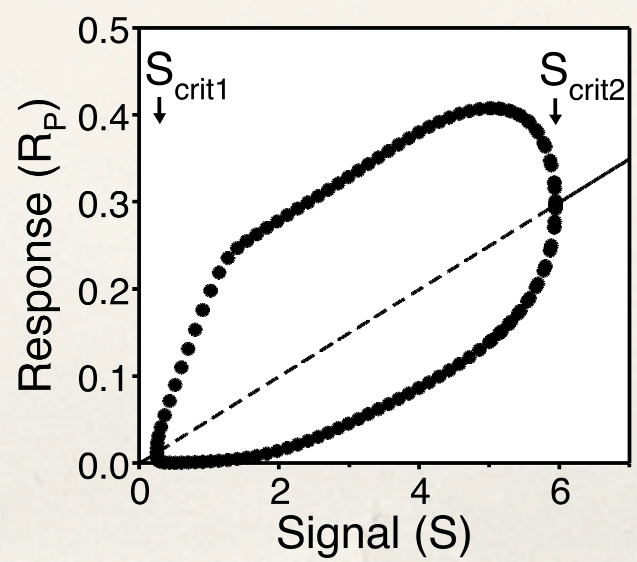
$$\frac{dX}{dt} = k_0 + k_1 S - k_2 X - k_7 R_P \cdot X$$

$$\frac{dY_P}{dt} = \frac{k_3 X (Y_T - Y_P)}{K_{m3} + (Y_T - Y_P)} - \frac{k_4 Y_P}{K_{m4} + Y_P}$$

$$\frac{dR_P}{dt} = \frac{k_5 Y_P (R_T - R_P)}{K_{m5} + (R_T - R_P)} - \frac{k_6 R_P}{K_{m6} + R_P}.$$

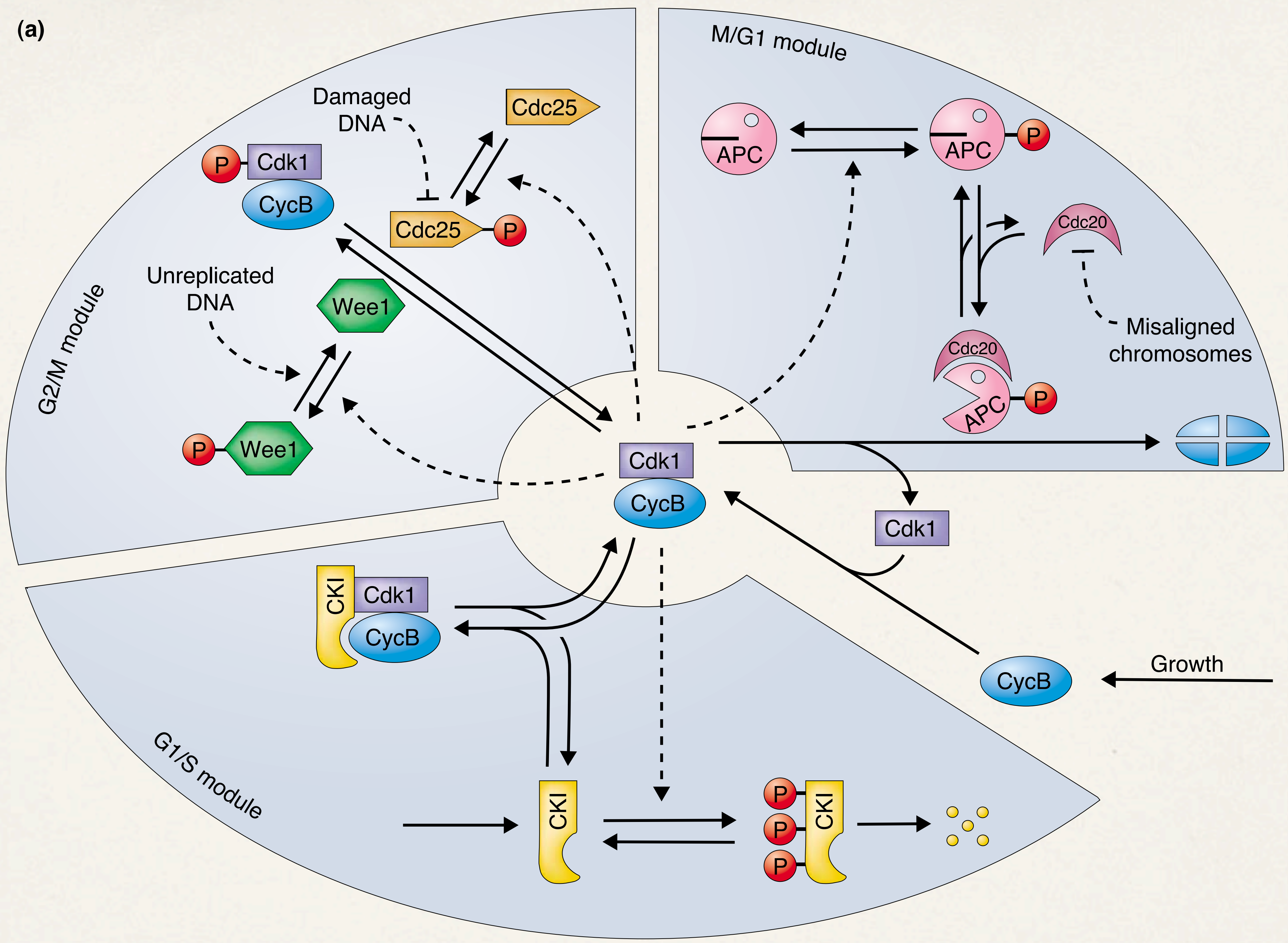
Two possible ways of inhibition



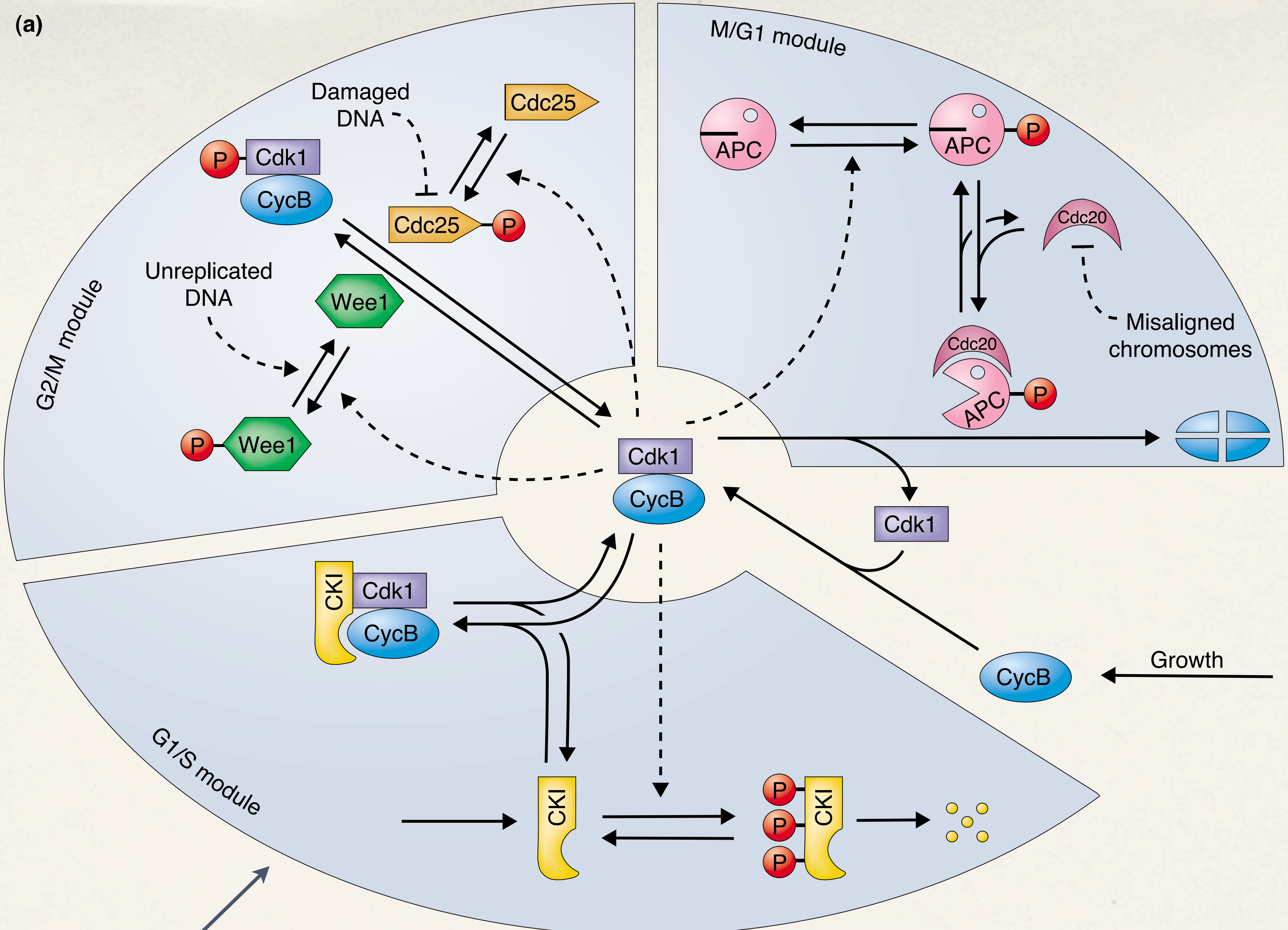


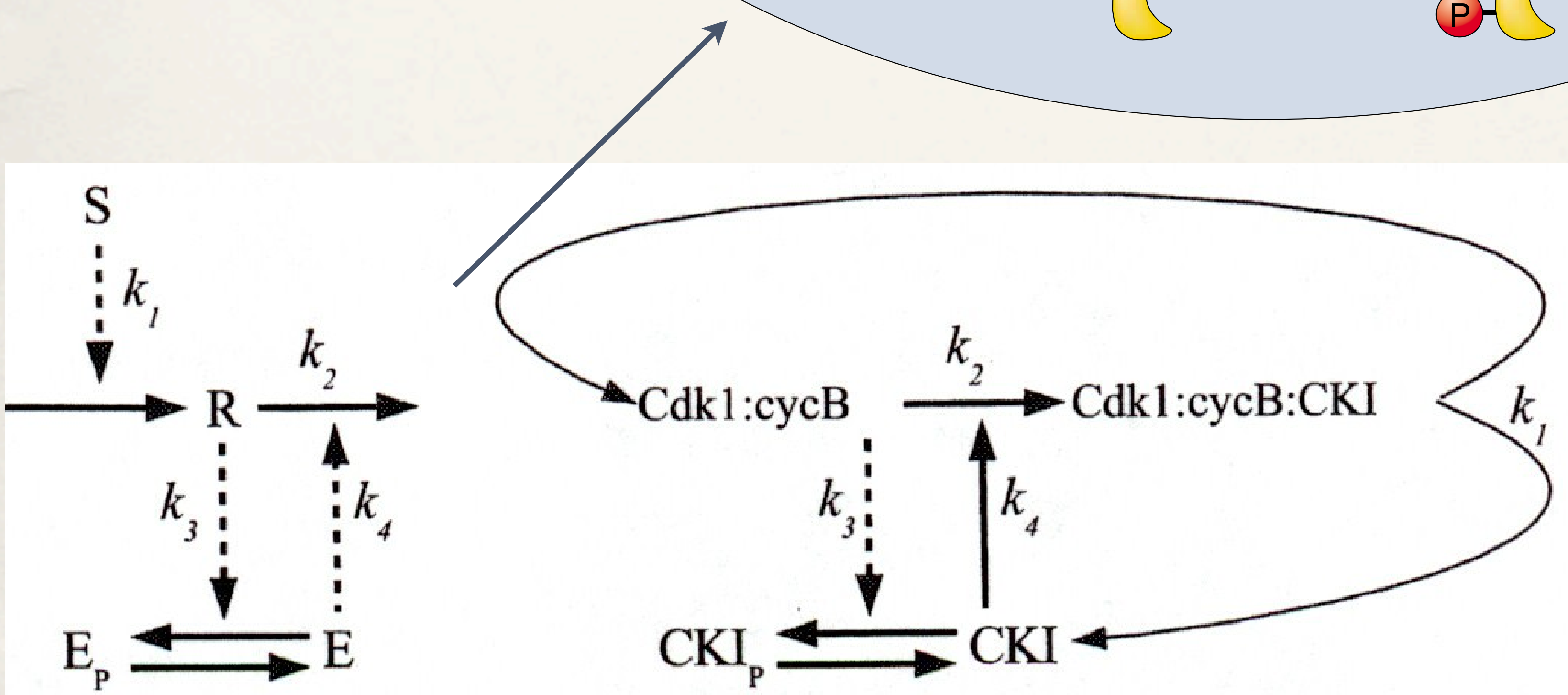
Steady-state is unstable between S_{crit1} and S_{crit2}; it oscillates between R_{Pmin} and R_{Pmax}.

Putting It All Together:
Cell Cycle Control System

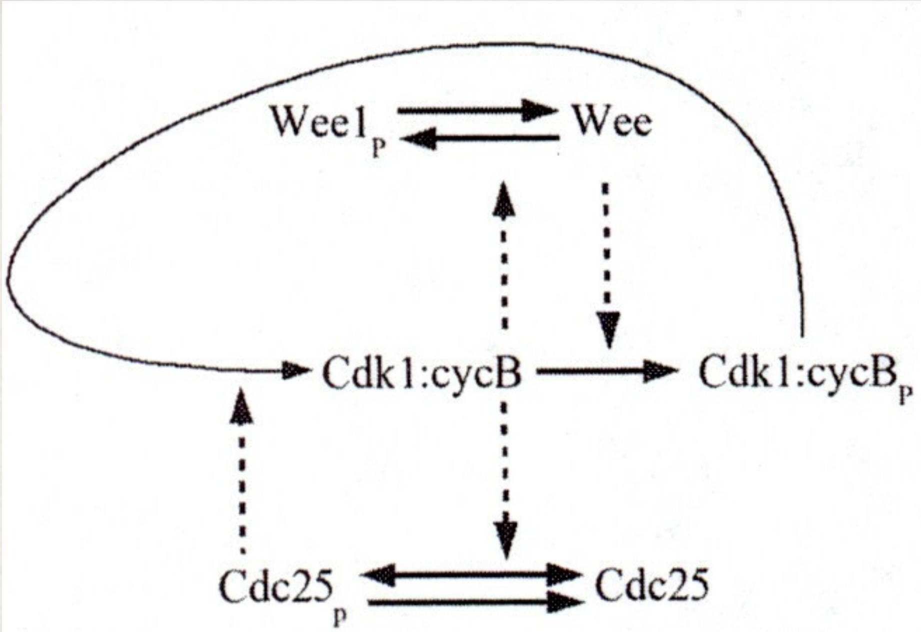


Wiring diagram for the cyclin-dependent kinase (Cdk) network regulating DNA synthesis and mitosis.

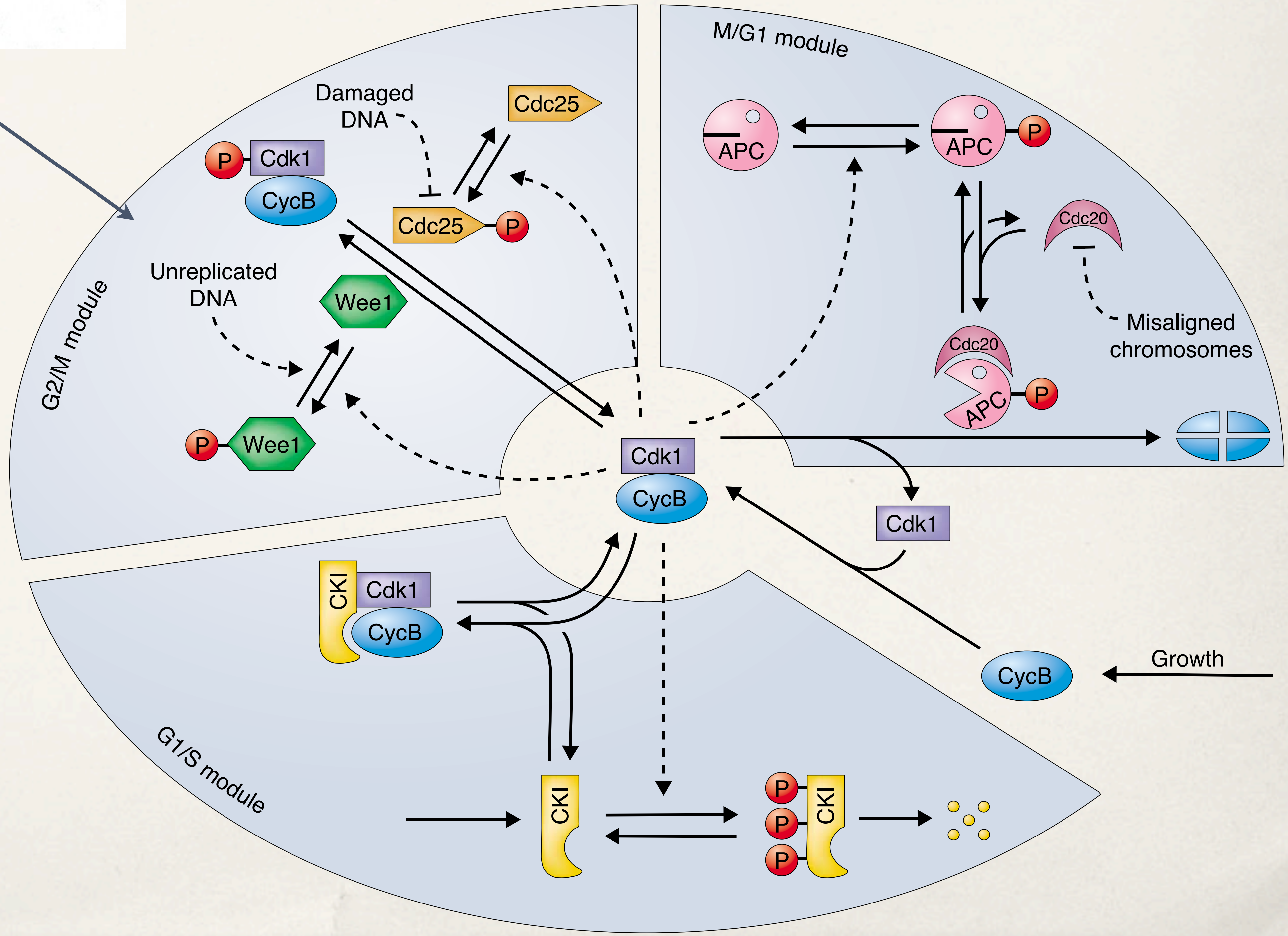




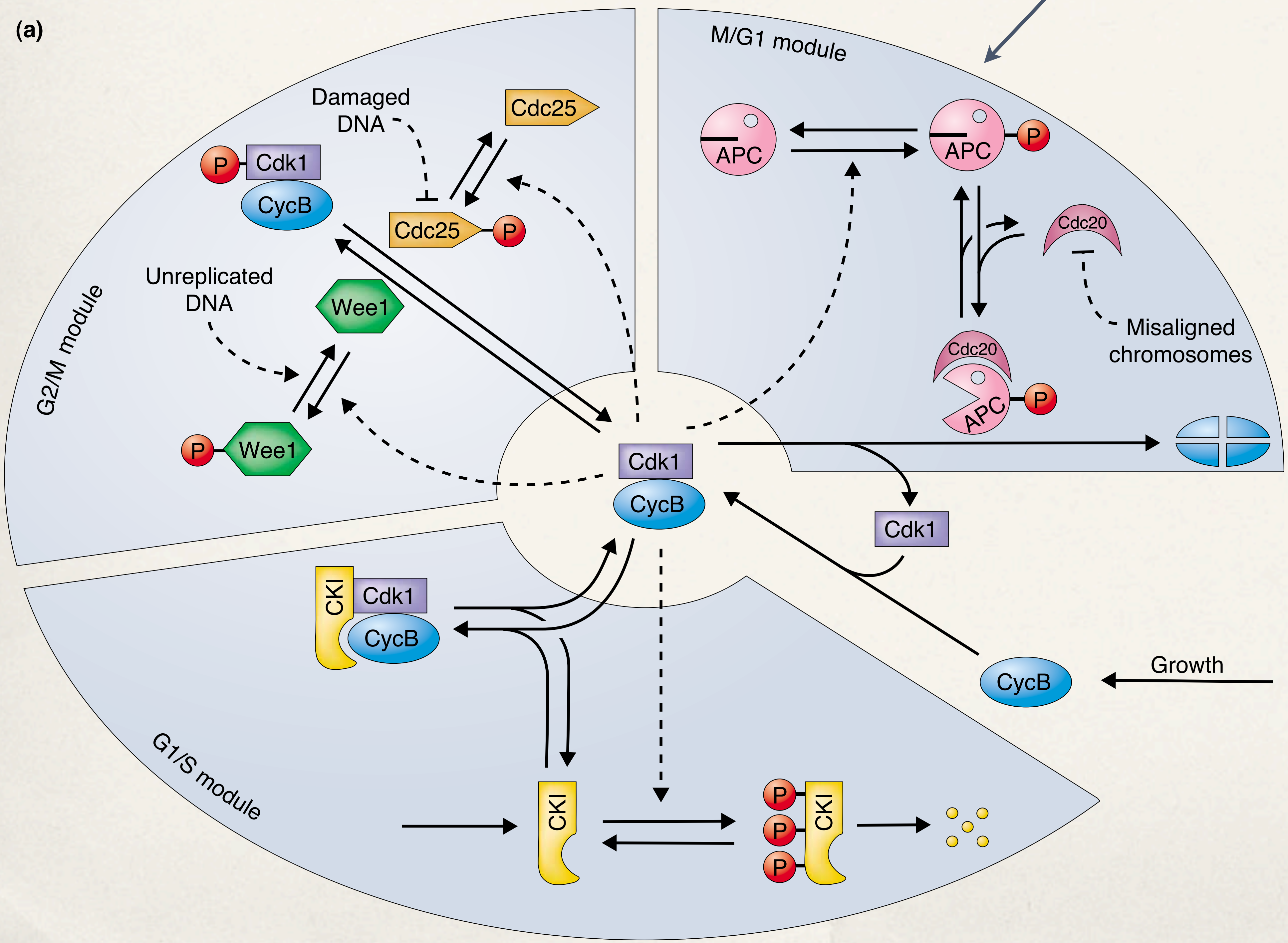
toggle-switch (mutual inhibition between Cdk1-cyclin B and CKI)



toggle-switch
(mutual activation between Cdk1-cyclin B and Cdc25, and mutual inhibition between Cdk1-cyclin B and Wee1)



oscillator, based on negative-feedback loop.
Cdk1-cyclin B activates the APC, which activates Cdc20, which degrades cyclin B.



Acknowledgment

- Material is based on the paper
  - *"Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell"*, Tyson *et al.*, Current Opinion in Cell Biology, 15: 221-231, 2003.