系统生物学

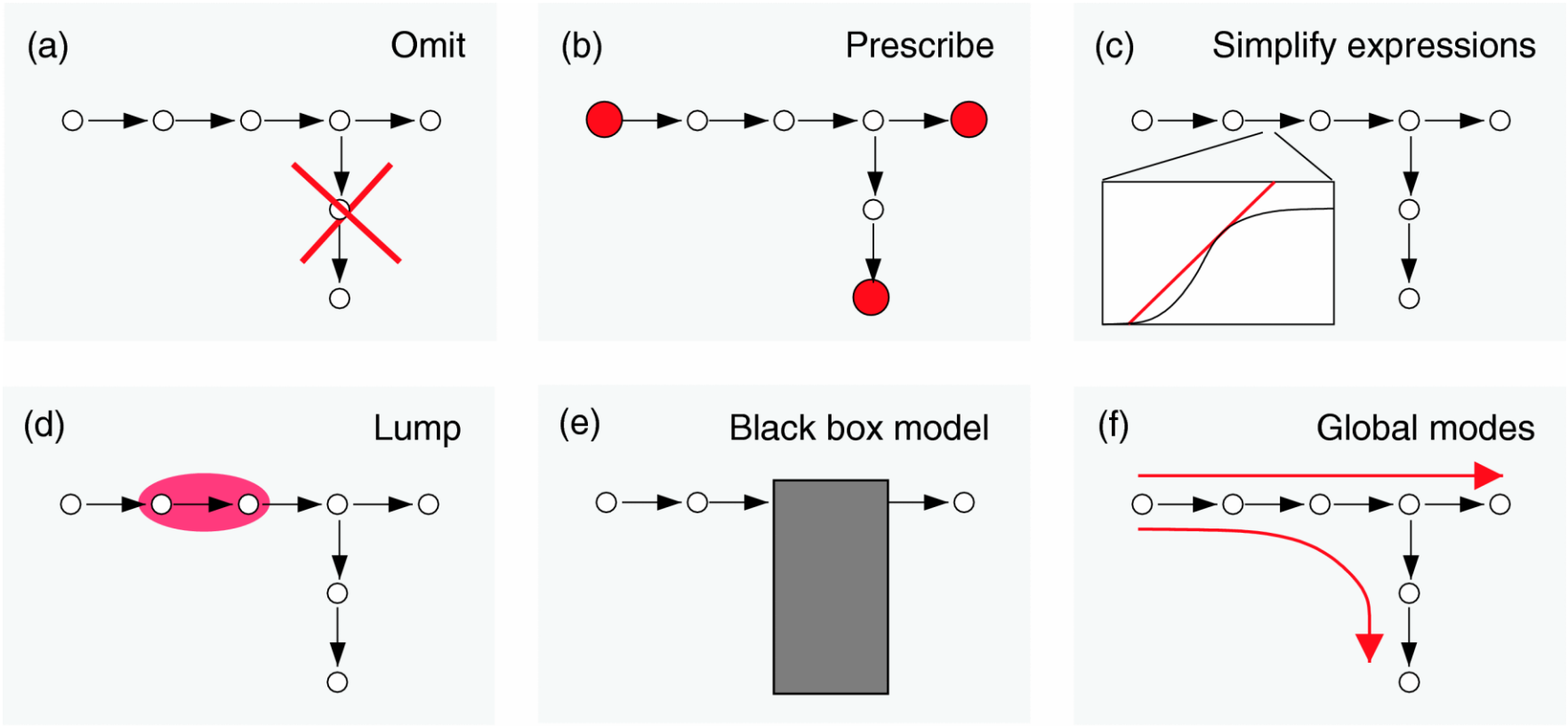
(Systems Biology)

马彬广

模型的化简与耦合

（第十三讲）

Simplification in Biochemical Models



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Simplification in Biochemical Models

Simplifications in biochemical models. The scheme shows a branched pathway of metabolites (circles) and reactions (arrows).
(a) Omitting substances or reactions.
(b) Predefining the values of concentrations or fluxes or relations between them.
(c) Simplifying the mathematical expressions (e.g., omitting terms in a kinetic law, using simplified kinetic laws , neglecting insensitive parameters).
(d) Lumping the substances, for instance, similar metabolites, protonation states of a metabolite, or metabolite concentrations in different compartments. Likewise, subsequent reactions in a pathway or elementary steps in a reaction can be replaced by a single reaction of the same velocity; for parallel reactions, like the action of isoenzymes, the velocities are summed up; for the two directions of a reaction, the velocities are subtracted.
(e) Replacing the model parts by a dynamic black-box model that mimics the input–output behavior.
(f) Describing the dynamic behavior by global modes (e.g., elementary flux modes or eigenmodes of the Jacobian).

模型的两个方面

正面：考虑进模型的那些因素；反面：模型忽略掉的那些因素。

Example 4.2: Stabilization by negative feedback

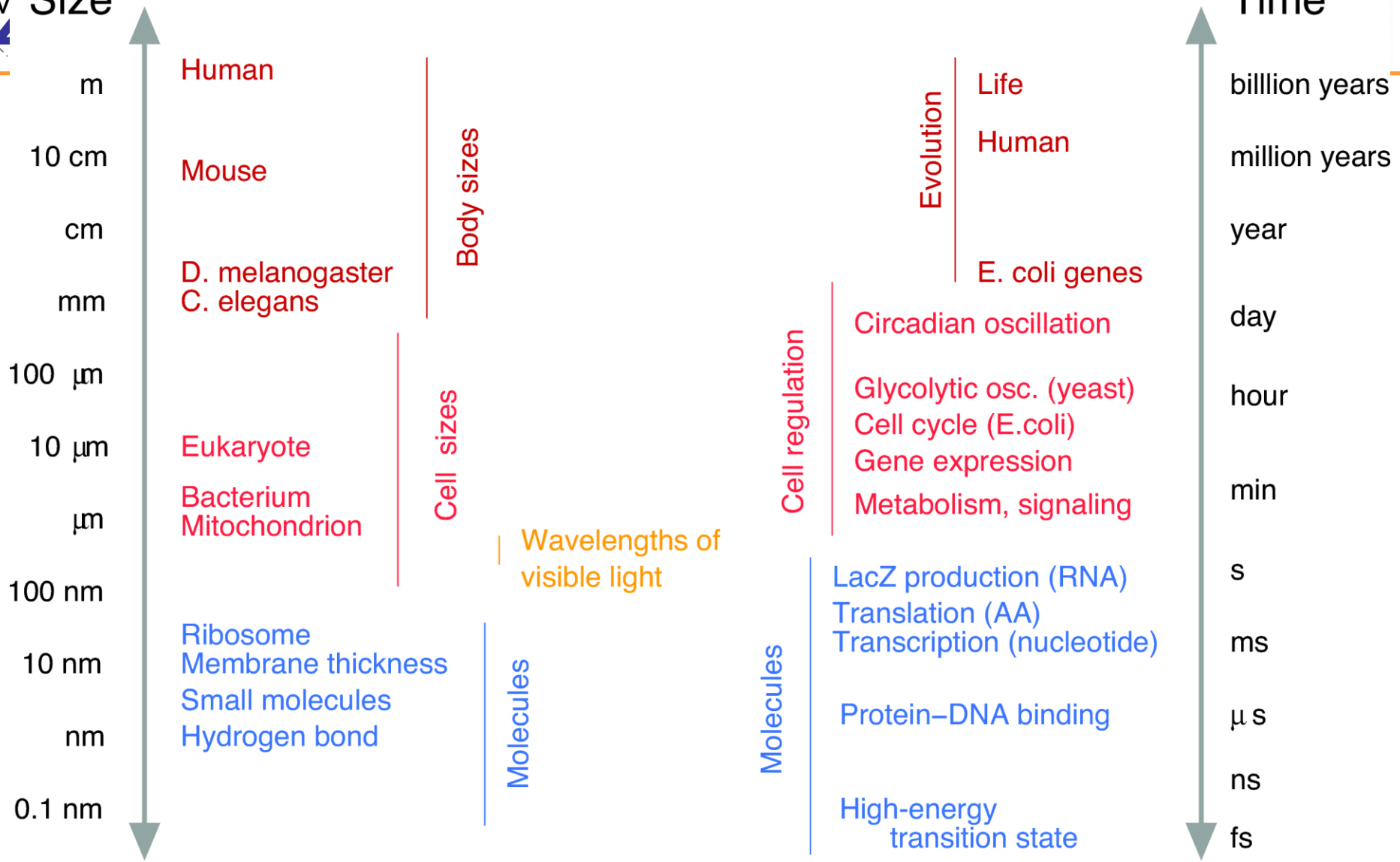
Consider a simple kinetic model [24]

$$\frac{ds}{dt} = \frac{a}{1 + s/K_I} - b\,s \tag{4.18}$$

of self-inhibited protein production (with the protein level s, maximal production rate a, inhibition constant K_I, and degradation constant b). The model predicts that the protein level can be stabilized against noise by self-inhibition. Without inhibition ($K_I \to \infty$), the Jacobian of the system reads $\boldsymbol{A} = -b$; with inhibition, the Jacobian $\boldsymbol{A} = -aK_I/(K_I + s^{st})^2 - b$ has a larger negative value, so s becomes more stable against small random perturbations. Becskei and Serrano [24] have approved this stabilization effect in an experiment with synthetic genetic circuits.

However, the experiment does not only test the model (4.18) itself – the positive statements –, but also all kinds of simplifying assumptions made: (i) in the model, details of transcription and translation, as well as stochastic effects due to small particle numbers, are ignored; (ii) the behavior of the protein level s is entirely determined by s itself and interactions with other processes are neglected; (iii) the model parameters are assumed to be constant while in reality, they may depend on the cell state, be noisy or influenced by s itself, thus forming an additional feedback loop.

生物系统的时空尺度



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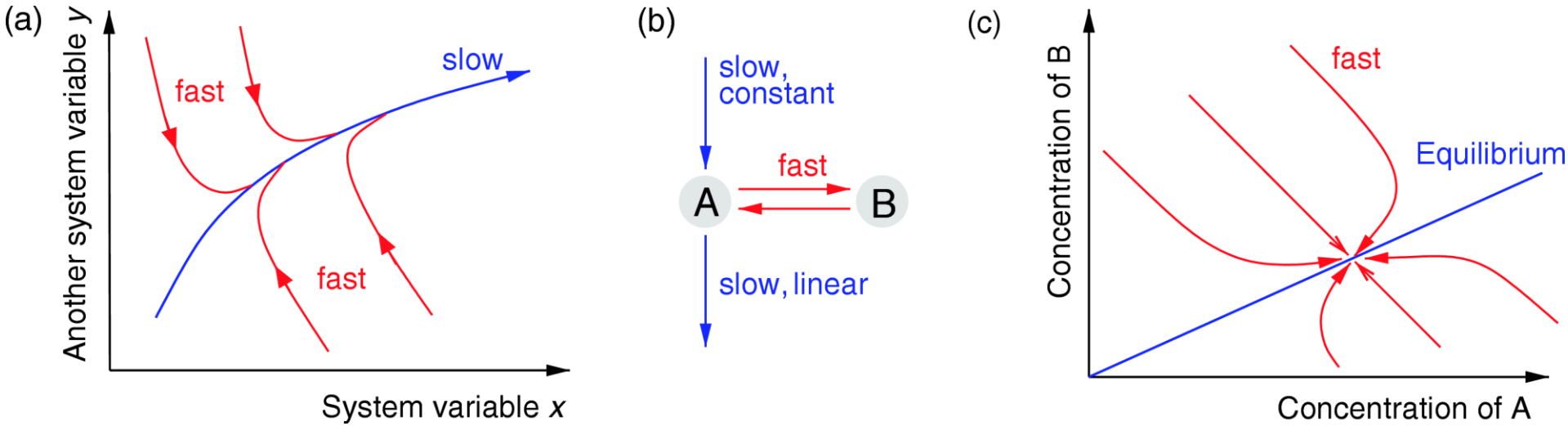
Time-Scale Separation



The dynamics of a system can be illustrated by its trajectories in state space. If the system state is attracted by a submanifold (in the two-dimensional case, a curve), trajectories starting from any point (red) will rapidly approach this manifold (blue). Later, the system will move slowly on the manifold, satisfying an algebraic equation.

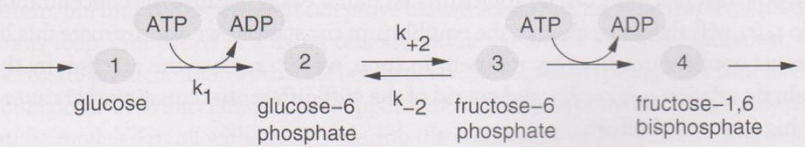
A small reaction system with different time scales. Fast conversion between metabolites A and B will keep their concentration ratio s_b/s_a close to the equilibrium constant K_{eq}, while slow production and degradation of A only changes the sum $sa+sb$. Schematic trajectories for the system shown in (b).

For any initial conditions, the concentrations s_A and s_B will rapidly approach the line $s_B/s_A = K_{eq}$ and then move slowly toward the steady state.

Time-Scale Separation

Example 4.3: Quasi-steady-state and quasi-equilibrium

We shall illustrate two types of approximation, quasi-steady state and quasi-equilibrium, with a simple model of upper glycolysis (see Section 3.1.2).



Glucose (GLC) is taken up at a rate ν_0 and converted subsequently into glucose-6-phosphate (G6P), fructose-6-phosphate (F6P), and fructose-1,6-bisphosphate (FBP), which is then consumed by the following steps of glycolysis. In this model, the cofactors ATP and ADP have fixed concentrations. With mass-action kinetics and a reversible reaction between G6P and F6P, the rate equations read:

$$\frac{ds_1}{dt} = \nu_0 - k_1 s_A s_1 \tag{4.21}$$

$$\frac{ds_2}{dt} = k_1 s_A s_1 - k_{+2} s_2 + k_{-2} s_3 \tag{4.22}$$

$$\frac{ds_3}{dt} = k_{+2} s_2 - k_{-2} s_3 - k_3 s_A s_3 \tag{4.23}$$

$$\frac{ds_4}{dt} = k_3 s_A s_3 - k_4 s_4. \tag{4.24}$$

The numbers refer to the metabolites and reactions in the scheme and s_A denotes the constant ATP concentration. We first assume that all reactions take place on a similar time scale, setting $k_{+2} = 2$ and all other rate constants and the ATP concentration to a value of 1 (arbitrary units). Figure 4.10(a) shows simulated concentration curves of GLC, G6P, F6P, and FBP; the initial concentrations are chosen to be zero. For the first 5 time units, the influx has a value of $\nu_0 = 2$, and the intermediate levels rise one after the other. Then, the influx is reduced to $\nu_0 = 1$, and the levels decrease again.

Time-Scale Separation

How would the system behave if either the first or the second reaction was very fast? The two scenarios can be approximated, respectively, by a quasi-steady-state for glucose or a quasi-equilibrium between G6P and F6P.

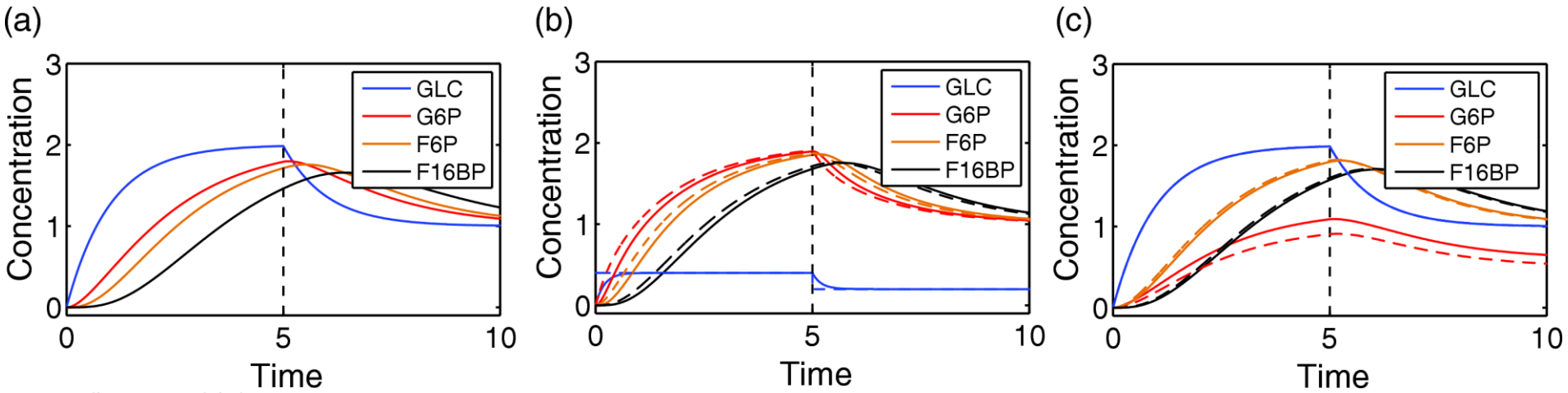
If k_1 is increased to a value of 5 (Figure 4.10(b)), glucose is rapidly consumed, so its steady-state level will stay low; due to its high turnover, glucose will also adapt almost instantaneously to changes of the input flux. This behavior can be approximated by a quasi-steady-state approximation for the slow time scale: we replace the glucose concentration in each time point by the steady-state value $s_1^{st}(t) = \nu_0(t)/(k_1 s_A)$ based on the current value of $\nu_0(t)$. This algebraic equation replaces the differential equation (4.21) for s_1. Formally, we could obtain the same result by setting the left-hand side of the differential equation to zero.

Next, we assume a rapid and reversible conversion between the hexoses G6P and F6P. We increase both rate constants at the same time by a large factor ($k_{+2} = 10$ and $k_{-2} = 5$ in Figure 4.10(c)) while keeping their ratio $k_{eq} = k_{+2}/k_{-2}$ fixed: in the simulation, the ratio of F6P to G6P levels rapidly approaches the equilibrium constant [F6P]/[G6P] $= s_3/s_2 = K_{eq}$. In the quasi-equilibrium approximation, we assume that this ratio is exactly maintained in every moment. By adding Eqs. (4.22) and (4.23), we obtain the equation

$$\frac{ds_{2+3}}{dt} = \frac{d(s_2 + s_3)}{dt} = k_1 s_A s_1 - k_3 s_A s_3. \qquad (4.25)$$

Given s_{2+3} and K_{eq}, we can substitute $s_3 = s_{2+3} K_{eq}/(1 + K_{eq})$ in Eq. (4.24) and obtain a simplified differential equation system in which the fast reaction does not

Simulation results for the model of upper glycolysis



(a) Results from the original model, showing levels of GLC, G6P, F6P, and FBP (abbreviations see text, time and concentrations measured in arbitrary units).

(b) Results from the model with fast glucose turnover $k1 = 5$ (solid lines) and the quasi-steady-state approximation (broken lines).

(c) Results from the model with fast reversible conversion G6P ↔ F6P (solid lines), parameters $k_{+2} = 10$, $k_{-2} = 5$ and the quasi-equilibrium approximation (broken lines).

Coupled Systems and Emergent Behavior

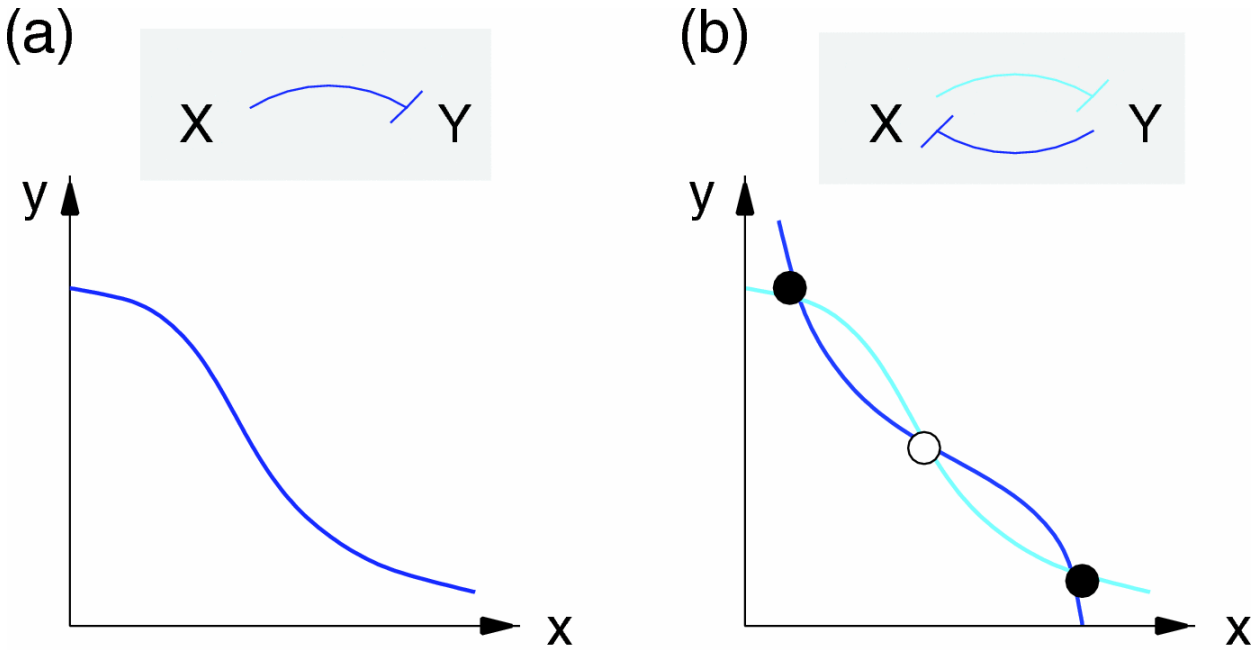
Example 4.4: Bistable switch

Let us consider two genes X and Y that mutually inhibit each other (Figure 4.11); we describe their levels x and y by the differential equation model

$$\frac{dx}{dt} = f(x, y)$$
$$\frac{dy}{dt} = g(x, y). \tag{4.33}$$

By setting the second equation to zero and solving for y, we obtain the steady-state value of y as a function of x. The curve $y^{st}(x)$ in Figure 4.11(a) is called the *nullcline* of y. Likewise, we obtain another nullcline $x^{st}(y)$ from the first equation. These nullclines represent response curves for the individual systems. When both systems are coupled, both steady-state requirements $y^{st} = f(x^{st})$ and $x^{st} = g(y^{st})$ have to be satisfied at the same time. We obtain three fixed points, two of which are stable, as indicated by the slopes of the nullclines. Due to the positive feedback loop, a bistable switch has emerged. The bistability is not a property of the individual genes X and Y – it is an systemic property which is only caused by their coupling.

Coupled Systems and Emergent Behavior



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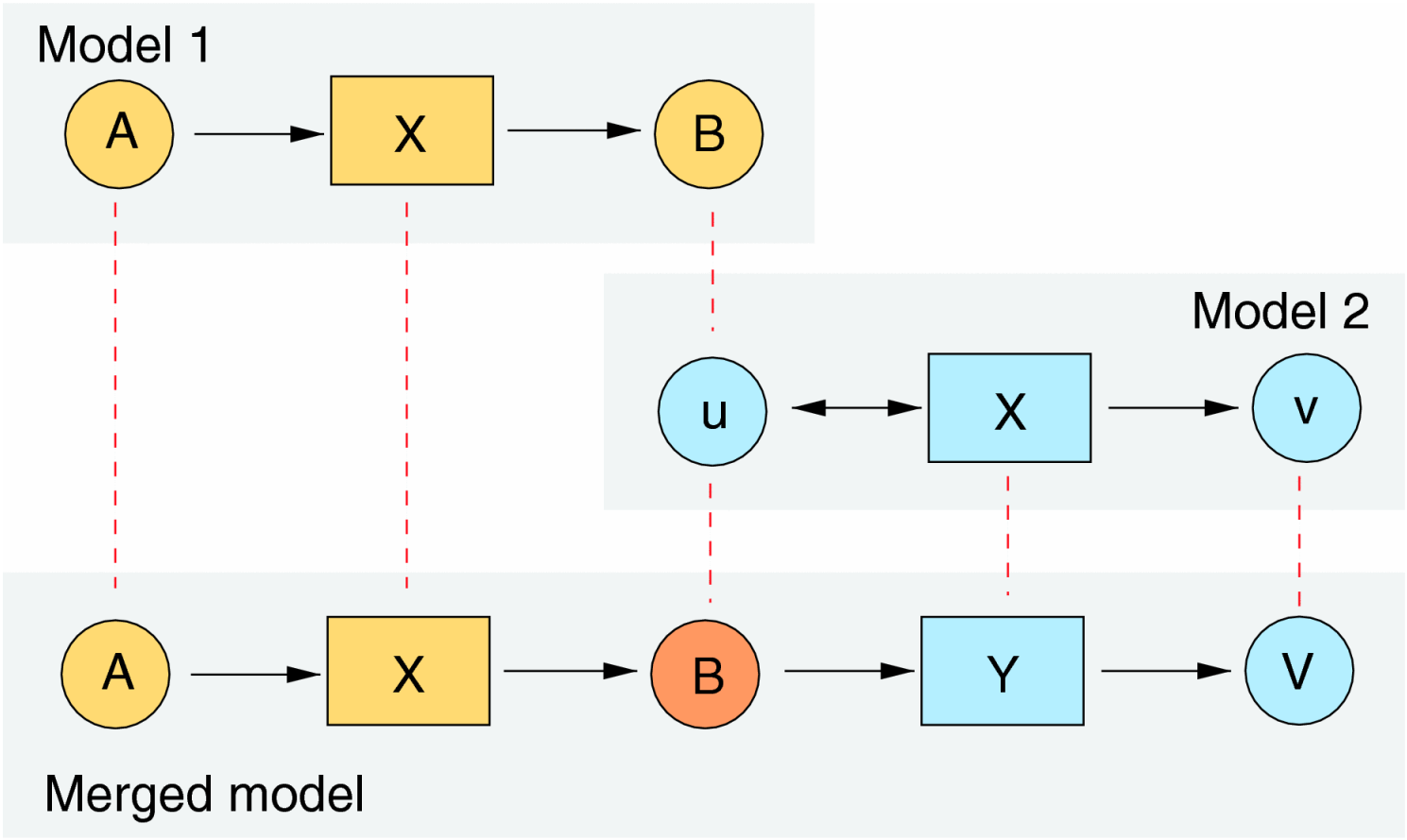
Bistability can emerge from mutual inhibition.
(a) A gene level *y* is modeled in isolation with another gene level *x* acting as a regulatory input. The steady-state level y^{st} (blue) depends on the given value of *x*.
(b) Two mutually interacting genes show bistability as an emergent property, with two stable fixed points (black dots) and one unstable fixed point (white dot) at the intersection of the two nullclines.

Merge Models



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What is a good model?

Agreement between model and data:	Represent the biological system:
1: Good data fit	3: Biological details
2: Good prediction	4: Reduce to key principles

Complexity

Simplicity

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