For the production terms, we may either assume constant values or (as mentioned above) rates that depend on the current cell state. The degradation terms might be assumed to be linearly dependent on the concentration of their substrates ($\nu_{d^*} = k_{d^*} \cdot R_*$). This may also be a first guess for the state changes of the receptor (e.g., $\nu_{is} = k_{is} \cdot R_i$). The receptor activation is dependent on the ligand concentration (or any other value related to the signal). A linear approximation of the respective rate is $\nu_{sa} = k_{sa} \cdot R_s \cdot L$. If the receptor is a dimer or oligomer, it might be sensible to include this information into the rate expression for receptor activation as $\nu_{sa} = k_{sa} \cdot R_s \cdot K_B^n \cdot L^n / (1 + K_B^n \cdot L^n)$, where K_B denotes the binding constant to the monomer and n the Hill coefficient (Section 2.1, Eq. (2.44)).

Example 3.1

An experimentally confirmed example for the activation of receptor and G protein of the pheromone pathway has been presented by Yi and colleagues [5] for the binding of the pheromone α-factor to the receptor Ste2 in yeast. Concerning the receptor activation dynamics, they report a susceptible and an active form of the receptor, but no inactive form ($R_i = 0$, $\nu_{*i} = \nu_{i^*} = 0$). The remaining rates are determined as follows:

$$\begin{aligned} \nu_{ps} &= k_{ps} \\ \nu_{ds} &= k_{ds} \cdot R_s \\ \nu_{da} &= k_{da} \cdot R_a \\ \nu_{sa} &= k_{sa} \cdot R_s \cdot L \\ \nu_{as} &= k_{as} \cdot R_a, \end{aligned} \tag{3.8}$$

with the following values for the rate constants: $k_{ps} = 4$ molecules per cell per second, $k_{ds} = 4 \times 10^{-4}\,s^{-1}$, $k_{da} = 4 \times 10^{-3}\,s^{-1}$, $k_{sa} = 2 \times 10^{6}\,M^{-1}\,s^{-1}$, and $k_{as} = 1 \times 10^{-2}\,s^{-1}$. The time course of receptor activation is depicted in Figure 3.12.

3.2.4 Structural Components of Signaling Pathways

Signaling pathways may constitute highly complex networks, but it has been discovered that they are frequently composed of typical building blocks. These components include Ras proteins, G protein cycles, phosphorelay systems, and MAP kinase cascades. In this section, we will discuss their general composition and function as well as modeling approaches.

3.2.4.1 G proteins

G proteins are essential parts of many signaling pathways. The reason for their name is that they bind the guanine nucleotides GDP and GTP. They are heterotrimers, i.e., they consist of three different subunits. Note the difference to small G proteins

consisting of one monomer, which are discussed below. G proteins are associated to cell surface receptors with a heptahelical transmembrane structure, the G protein-coupled receptors (GPCR). Signal transduction cascades involving (i) such a transmembrane surface receptor, (ii) an associated G protein, and (iii) an intracellular effector that produces a second messenger play an important role in cellular communication and are well-studied [6, 7]. In humans, GPCR mediate responses to light, flavors, odors, numerous hormones, neurotransmitters, and other signals [8–10]. In unicellular eukaryotes, receptors of this type mediate signals that affect such basic processes as cell division, cell–cell fusion (mating), morphogenesis, and chemotaxis [8, 11–13].

The cycle of G protein activation and inactivation is shown in Figure 3.13. When GDP is bound, the G protein α subunit (Gα) is associated with the G protein βγ heterodimer (Gβγ) and is inactive. Ligand binding to a receptor promotes guanine nucleotide exchange; Gα releases GDP, binds GTP, and dissociates from Gβγ. The dissociated subunits Gα or Gβγ, or both, are then free to activate target proteins (downstream effectors), which initiates signaling. When GTP is hydrolyzed, the subunits are able to reassociate. Gβγ antagonizes receptor action by inhibiting guanine nucleotide exchange. Regulator of G protein signaling (RGS) proteins bind to Gα, stimulate GTP hydrolysis, and thereby reverse G protein activation. This general scheme also holds for the regulation of small monomeric Ras-like GTPases, such as Rho. In this case, the receptor, Gβγ, and RGS are replaced by GEF and GAP (see below).

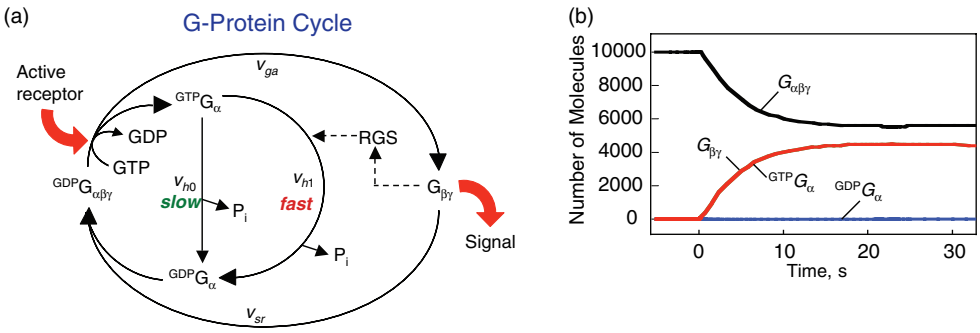

Figure 3.13 Activation cycle of G protein. (a) Without activation, the heterotrimeric G protein is bound to GPD. Upon activation by the activated receptor, an exchange of GDP with GTP occurs and the G protein is divided into GTP-bound Gα and the heterodimer Gβγ. Gα-bound GTP is hydrolyzed, either slowly in reaction v_{h0} or fast in reaction v_{h1} supported by the RGS protein. GDP-bound Gα can reassociate with Gβγ (reaction v_{sr}). (b) Time course of G protein activation. The total number of molecules is 10,000. The concentration of GDP-bound Gα is low for the whole period due to fast complex formation with the heterodimer Gβγ.

Direct targets include different types of effectors, such as adenylyl cyclase, phospholipase C, exchange factors for small GTPases, some calcium and potassium channels, plasma membrane Na^+/H^+ exchangers, and certain protein kinases [6, 14–16]. Typically, these effectors produce second messengers or other biochemical changes that lead to stimulation of a protein kinase or a protein kinase cascade (or, as mentioned, are themselves a protein kinase). Signaling persists until GTP is hydrolyzed to GDP and the Gα and Gβγ subunits reassociate, completing the cycle of activation. The strength of the G protein–initiated signal depends on (i) the rate of nucleotide exchange, (ii) the rate of spontaneous GTP hydrolysis, (iii) the rate of RGS-supported GTP hydrolysis, and (iv) the rate of subunit reassociation. RGS proteins act as GTPase-activating proteins (GAPs) for a variety of different Gα classes. Thereby, they shorten the lifetime of the activated state of a G protein, and contribute to signal cessation. Furthermore, they may contain additional modular domains with signaling functions and contribute to diversity and complexity of the cellular signaling networks [17–20].

Example 3.2

The model of the heterotrimeric G protein cycle of the yeast pheromone pathway was already mentioned in Example 3.1 and it is linked to the receptor activation model via the concentration of the active receptor. The G protein cycle model comprises two ODEs and two algebraic equations for the mass conservation of the subunits Gα and Gβγ:

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} G_{\alpha\beta\gamma} &= -\nu_{\mathrm{ga}} + \nu_{\mathrm{sr}} \\ \frac{\mathrm{d}}{\mathrm{d}t} G_{\alpha} GTP &= \nu_{\mathrm{ga}} - \nu_{\mathrm{h0}} - \nu_{\mathrm{h1}} \\ G_{\mathrm{total}\alpha} &= G_{\alpha\beta\gamma} + G_{\alpha} GTP + G_{\alpha} GDP \\ G_{\mathrm{total}\beta\gamma} &= G_{\alpha\beta\gamma} + G_{\beta\gamma}. \end{aligned} \tag{3.9}$$

The rate equations for the G protein activation, ν_{ga}, the hydrolysis of $G_{\alpha}GTP$, ν_{h0} and ν_{h1}, and the subunit reassociation, ν_{sr}, follow simple mass action kinetics:

$$\begin{aligned} \nu_{\mathrm{ga}} &= k_{\mathrm{ga}} \cdot R_{\mathrm{a}} \cdot G_{\alpha\beta\gamma} \\ \nu_{\mathrm{h}i} &= k_{\mathrm{h}i} \cdot G_{\alpha} GTP, \quad i = 0, 1 \\ \nu_{\mathrm{sr}} &= k_{\mathrm{sr}} \cdot G_{\beta\gamma} \cdot G_{\alpha} GDP. \end{aligned} \tag{3.10}$$

The parameters are $k_{\mathrm{ga}} = 1 \times 10^{-5}$ (molecule per cell)$^{-1}$ s^{-1}, $k_{\mathrm{h0}} = 0.004\,\mathrm{s}^{-1}$, $k_{\mathrm{h1}} = 0.11\,\mathrm{s}^{-1}$, and $k_{\mathrm{sr}} = 1$(molecule per cell)$^{-1}$ s^{-1}. Note that in the original work, two different yeast strains have been considered. For the strains with a constantly active RGS (*SST2*$^+$) or with a deletion of RGS (*sst2*Δ), the rate constants k_{h1} and k_{h0} have been set to zero, respectively. The time courses are shown in Figure 3.13.

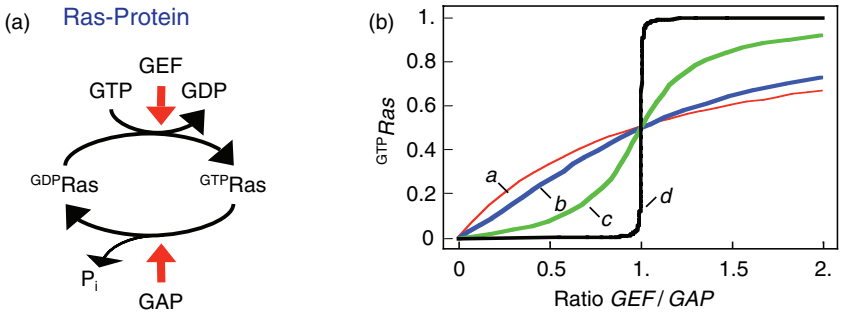

Figure 3.14 The Ras activation cycle. (a) Wiring diagram: GEF supports the transition form GDP-bound to GTP-bound states to activate Ras, while GAP induces hydrolysis of the bound GTP resulting in Ras deactivation. (b) Steady states of active Ras depending on the concentration ratio of its activator GEF and the inhibitor GAP. We compare the behavior for a model with mass action kinetics (curve a) with the behavior obtained with Michaelis–Menten kinetics for decreasing values of the K_m-value (curves b–d). The smaller the K_m-value, the more sigmoidal the response curve, leading to an almost steplike shape in the case of very low K_m-values. Parameters: $Ras_{total} = RasGTP + RasGDP = 1$, $k_1 = k_2 = 1$ (all curves), (b) $K_{m1} = K_{m2} = 1$, (c) $K_{m1} = K_{m2} = 0.1$, (d) $K_{m1} = K_{m2} = 0.001$.

3.2.4.2 Small G proteins

Small G proteins are monomeric G proteins with molecular weight of 20–40 kDa. Like heterotrimeric G proteins, their activity depends on the binding of GTP. More than a hundred small G proteins have been identified. They belong to five families: Ras, Rho, Rab, Ran, and Arf. They regulate a wide variety of cell functions as biological timers that initiate and terminate specific cell functions and determine the periods of time [21].

Ras proteins cycle between active and inactive states (Figure 3.14). The transition from GDP-bound to GTP-bound states is catalyzed by a guanine nucleotide exchange factor (GEF), which induces exchange between the bound GDP and the cellular GTP. The reverse process is facilitated by a GAP, which induces hydrolysis of the bound GTP. Its dynamics can be described with the following equation with appropriate choice of the rates v_{GEF} and v_{GAP}:

$$\begin{aligned} &\frac{d}{dt} RasGTP = -\frac{d}{dt} RasGDP = v_{GEF} - v_{GAP} \\ &v_{GEF} = \frac{k_1 \cdot GEF \cdot RasGDP}{(K_{m1} + RasGDP)} \quad \text{and} \quad v_{GAP} = \frac{k_2 \cdot GAP \cdot RasGTP}{(K_{m2} + RasGTP)}. \end{aligned} \tag{3.11}$$

Figure 3.14 illustrates the wiring of a Ras protein and the dependence of its activity on the concentration ratio of the activating GEF and the deactivating GAP.

Mutations of the *Ras* protooncogenes (H-*Ras*, N-*Ras*, K-*Ras*) are found in many human tumors. Most of these mutations result in the abolishment of normal GTPase activity of *Ras*. The Ras mutants can still bind to GAP, but cannot catalyze GTP hydrolysis. Therefore, they stay active for a long time.