Chapter 6
Computing Theoretical Drugs in the Two-Dimensional Case

Let us briefly recall the difficulty we want to overcome with the theoretical drug. The difficulty is that in the prototypical reaction defined by the Markov model

$$C \underset{k_{co}}{\overset{k_{oc}}{\leftrightarrows}} O$$

the rates may change under various mutations. One case that we have focused on in these notes is CO-mutations where the reaction rate from C to O is increased. The reaction of a CO-mutation takes the form

$$C \underset{\mu k_{co}}{\overset{k_{oc}}{\leftrightarrows}} O,$$

where we assume that $\mu \geqslant 1$ is a constant. We refer to this constant as the mutation severity index and the mutation is typically worse the larger the value of μ; furthermore, $\mu = 1$ refers to the wild type case. Our aim is to devise a theoretical drug of the form

$$B_c \underset{k_{bc}}{\overset{k_{cb}}{\leftrightarrows}} C \underset{\mu k_{co}}{\overset{k_{oc}}{\leftrightarrows}} O \underset{k_{ob}}{\overset{k_{bo}}{\leftrightarrows}} B_o,$$

where the constants k_{bc}, k_{cb}, k_{bo}, and k_{ob} are used to tune the drug such that the effect of the mutation is reduced as much as possible. As above, we will consider blockers associated with the closed state, which means that $k_{ob} = 0$, or blockers associated with the open state, which means that $k_{cb} = 0$. The model and discretization parameters used throughout this chapter are given in Table 6.1.

A. Tveito, G.T. Lines, *Computing Characterizations of Drugs for Ion Channels and Receptors Using Markov Models*, Lecture Notes in Computational Science and Engineering 111, DOI 10.1007/978-3-319-30030-6_6

Table 6.1 Parameters reused from the previous chapter (i.e., Table 5.1)

v_d	1 ms^{-1}
v_r	0.1 ms^{-1}
v_s	0.01 ms^{-1}
c_0	0.1 μM
c_1	1,000 μM
k_{co}	1 ms^{-1}
k_{oc}	1 ms^{-1}
Δt	0.001 ms
Δx	0.92 μM
Δy	9.3 μM

6.1 Effect of the Mutation in the Two-Dimensional Case

When the effect of the mutation is taken into account, the probability density functions are governed by the system

$$\frac{\partial \rho_o}{\partial t} + \frac{\partial}{\partial x}\left(a_o^x \rho_o\right) + \frac{\partial}{\partial y}\left(a_o^y \rho_o\right) = \mu k_{co}\rho_c - k_{oc}\rho_o, \tag{6.1}$$

$$\frac{\partial \rho_c}{\partial t} + \frac{\partial}{\partial x}\left(a_c^x \rho_c\right) + \frac{\partial}{\partial y}\left(a_c^y \rho_c\right) = k_{oc}\rho_o - \mu k_{co}\rho_c, \tag{6.2}$$

where we recall that the fluxes are given by

$$\begin{aligned} a_o^x &= v_r\,(y - x) + v_d\,(c_0 - x)\,, \\ a_o^y &= v_r\,(x - y) + v_s\,(c_1 - y)\,, \\ a_c^x &= v_d\,(c_0 - x)\,, \\ a_c^y &= v_s\,(c_1 - y) \end{aligned} \tag{6.3}$$

(see page 102). In Fig. 6.1, we compare the solution of this system when $\mu = 1$ (wild type) and $\mu = 3$ (mutant) and in Table 6.2 we give the statistics of the solutions. The total open probability increases from 0.430 for the wild type to 0.743 for the mutant. In addition, the expected concentrations of both the dyad and the junctional sarcoplasmic reticulum (JSR) decrease considerably. In the one-dimensional (1D) case we observed that the variability of the solution decreased when the mutation was introduced. This observation seems to carry over to the two-dimensional (2D) case.

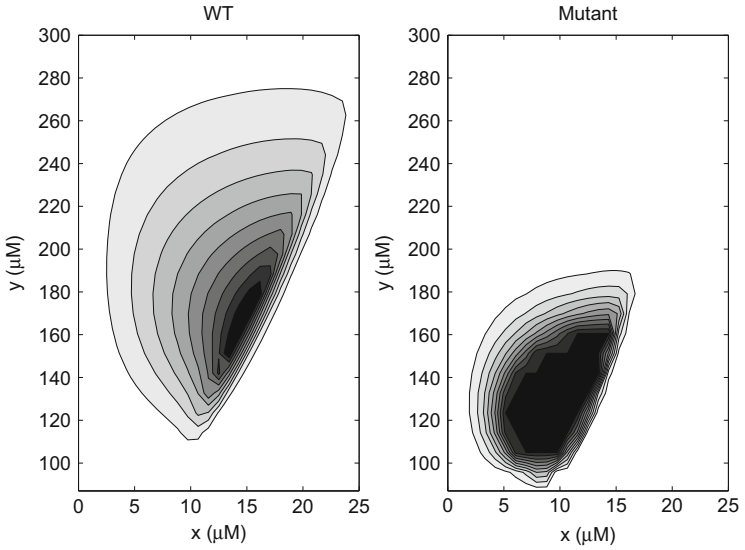

Fig. 6.1 The open state probability density function for the wild type case (*left*) and the mutant case (*right*, $\mu = 3$)

Table 6.2 Properties of the open probability density function in the wild type and mutant cases

Case	π_o	E_{x_o}	E_{y_o}	σ_{x_o}	σ_{y_o}
Wild type	0.430	12.63	202.4	4.948	46.27
Mutant	0.743	9.64	131.7	2.419	18.90

6.2 A Closed State Drug

In the 1D case, we were able to compute a characterization of the closed state drug based on considering the equilibrium solution of the reaction scheme. Since the reaction scheme is the same in the 1D and 2D problems, we can use exactly the same characterization as above. Let us first recall that the reaction scheme of the closed state drug takes the form

$$B \underset{k_{bc}}{\overset{k_{cb}}{\leftrightarrows}} C \underset{\mu k_{co}}{\overset{k_{oc}}{\leftrightarrows}} O.$$

We found above (see (3.9) on page 59) that the parameters of the closed state blocker should be related as

$$k_{cb} = (\mu - 1)k_{bc}, \tag{6.4}$$

so the optimal value of k_{bc} remains to be determined. To find the optimal value of this parameter, we need to extend the system (6.1) and (6.2) to account for the

theoretical drug. When the closed state blocker is added, the steady state version of the probability density system reads

$$\frac{\partial}{\partial x}\left(a_o^x \rho_o\right) + \frac{\partial}{\partial y}\left(a_o^y \rho_o\right) = \mu k_{co}\rho_c - k_{oc}\rho_o, \tag{6.5}$$

$$\frac{\partial}{\partial x}\left(a_c^x \rho_c\right) + \frac{\partial}{\partial y}\left(a_c^y \rho_c\right) = k_{oc}\rho_o - \left(\mu k_{co} + (\mu - 1)\, k_{bc}\right)\rho_c + k_{bc}\rho_b, \tag{6.6}$$

$$\frac{\partial}{\partial x}\left(a_c^x \rho_b\right) + \frac{\partial}{\partial y}\left(a_c^y \rho_b\right) = (\mu - 1)\, k_{bc}\rho_c - k_{bc}\rho_b. \tag{6.7}$$

Our aim is now to compute the value of the single parameter k_{bc} such that the open probability density function defined by the system (6.5)–(6.7) is as close as possible to the solution of the system (6.1) and (6.2) in the case of $\mu = 1$ (i.e., the wild type case). In other words, we want to use the drug to repair the effect of the mutations in the sense that we want the open probability densities to be as close as possible to the wild type open probability densities.

In Fig. 6.2 we show the solution of the system (6.5)–(6.7) using $\mu = 3$ and $k_{bc} = 0.01$, 0.1, 1, and 10 ms^{-1}. As expected, we note that the solution becomes increasingly similar to the wild type solution (see Fig. 6.1) as k_{bc} increases.

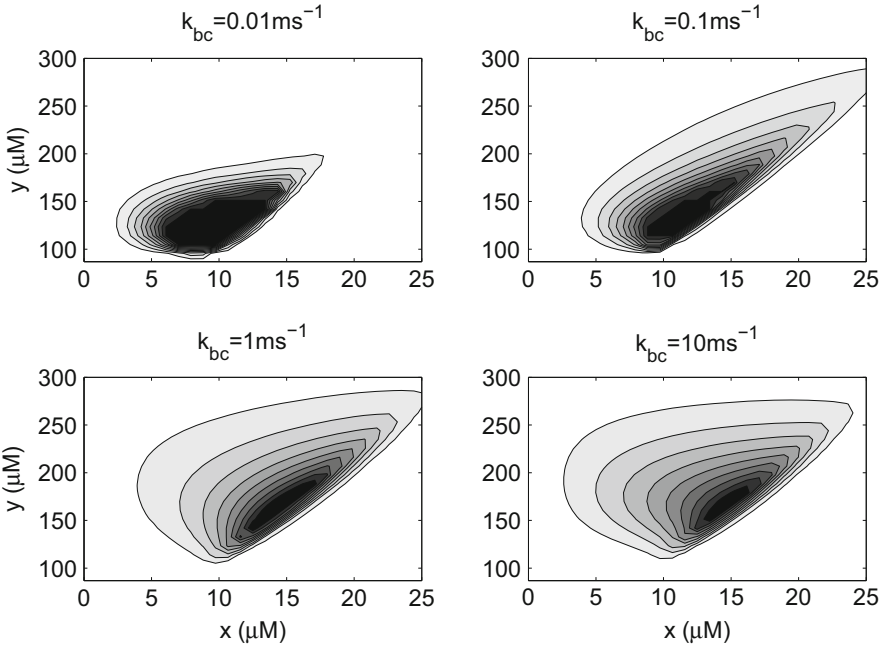

Fig. 6.2 Closed state blocker applied to the mutant case ($\mu = 3$). As the value k_{bc} increases, the probability density function approaches the wild type solution

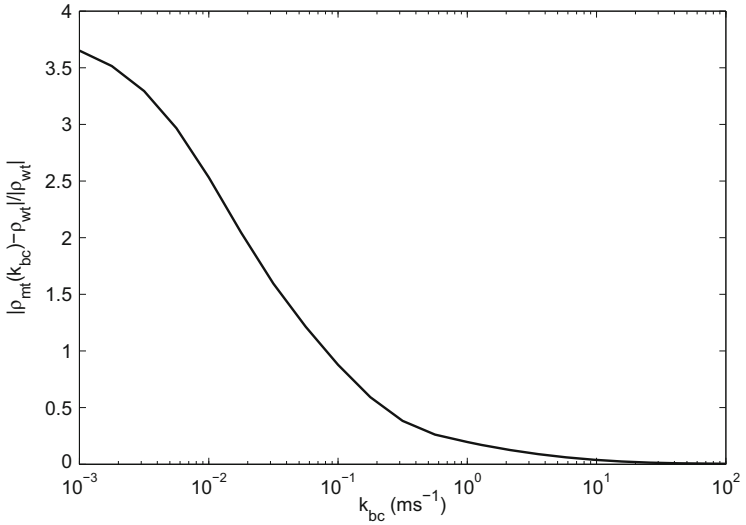

Fig. 6.3 The solution with the closed state blocker approaches the wild type case as k_{bc} increases

6.2.1 Convergence as k_{bc} Increases

Again we observe that the theoretical closed state blocker becomes more efficient for larger values of k_{bc}. To obtain a more precise impression of the convergence, we compute the norm of the difference between the open probability of the wild type case and the open probability of the solution of the system (6.5)–(6.7) as a function of k_{bc} using the norm defined by (2.40) on page 46. The result is shown in Fig. 6.3 and we again observe that, when k_{bc} becomes sufficiently large, the effect of the mutation is repaired completely.

6.3 An Open State Drug

The reaction scheme of an open state blocker for a mutant is

$$C \underset{\mu k_{co}}{\overset{k_{oc}}{\leftrightarrows}} O \underset{k_{ob}}{\overset{k_{bo}}{\leftrightarrows}} B.$$

We learned above that we had limited success in using the equilibrium solution to derive an optimal characterization of the open state drug. We will therefore directly optimize the two parameters k_{bo} and k_{ob}.

6.3.1 Probability Density Model for Open State Blockers in 2D

The probability density model in the presence of an open state drug is

$$\frac{\partial}{\partial x}\left(a_o^x \rho_o\right) + \frac{\partial}{\partial y}\left(a_o^y \rho_o\right) = \mu k_{co}\rho_c - (k_{oc} + k_{ob})\rho_o + k_{bo}\rho_b, \tag{6.8}$$

$$\frac{\partial}{\partial x}\left(a_c^x \rho_c\right) + \frac{\partial}{\partial y}\left(a_c^y \rho_c\right) = k_{oc}\rho_o - \mu k_{co}\rho_c, \tag{6.9}$$

$$\frac{\partial}{\partial x}\left(a_c^x \rho_b\right) + \frac{\partial}{\partial y}\left(a_c^y \rho_b\right) = k_{ob}\rho_o - k_{bo}\rho_b. \tag{6.10}$$

In Fig. 6.4, we show the cost function defined by the norm (see (2.40) on page 46) of the difference between the open probability density function of the wild type (solution of (6.1) and (6.2) with $\mu = 1$) and the open probability density function of the solution of the system (6.8)–(6.10) with $\mu = 3$. By minimizing the cost function, using Matlab's *Fminsearch* with default parameters and $k_{ob} = k_{bo} = 1$ as an initial guess, we find that an optimal open state blocker is given by

$$k_{ob} = 0.3225\ \text{ms}^{-1},\ k_{bo} = 0.3346\ \text{ms}^{-1}. \tag{6.11}$$

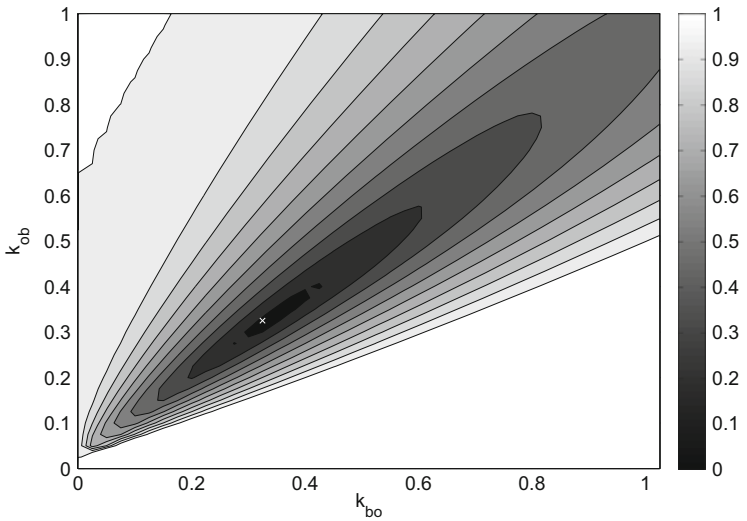

Fig. 6.4 Relative difference between the wild type and the mutant with an open state blocker for the case $\mu = 3$. There is a minimum around $(k_{bo}, k_{ob}) \approx (0.3, 0.3)\ \text{ms}^{-1}$ marked by a small ×

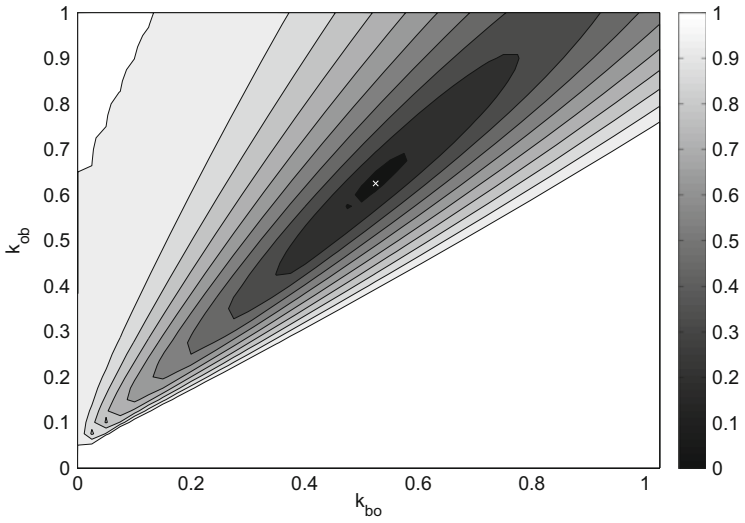

Fig. 6.5 Relative difference between the wild type and the mutant with an open state blocker for the case $\mu = 10$. There is a minimum around $(k_{bo}, k_{ob}) = (0.53, 0.63)$ ms^{-1}

6.3.1.1 Does the Optimal Theoretical Drug Change with the Severity of the Mutation?

One issue here is to see if the drug changes with the mutation severity index. Numerical experiments show that the optimal drug does change. In Fig. 6.5, we show the case in which $\mu = 10$ and the optimum has shifted compared to Fig. 6.4.

6.4 Statistical Properties of the Open and Closed State Blockers in 2D

We introduced statistical properties of probability density functions in Sect. 4.2 (see page 72). In Sect. 4.6 (page 88), we observed that, for the 1D release problem, the closed state blocker completely repaired the statistical properties of the open state probability density functions. In addition, an optimized version of an open state blocker gave good results, but it was unable to repair the standard deviation of the open state probability density functions for the particular CO-mutations we considered.

The statistical properties of the solutions for 2D release are summarized in Table 6.3. The results are quite similar to the 1D case. Again, for the CO-mutations, the closed state blocker improves as the value of k_{bc} increases and the optimized version of the open state blocker also provides good results.

Table 6.3 Statistical properties of the open probability density function in the mutant case when a blocker is applied. For the mutant case, we use $\mu = 3$

Case	π_o	E_{x_o}	E_{y_o}	σ_{x_o}	σ_{y_o}
Closed blocker, k_{bc}= 0.01	0.547	10.55	144.2	4.726	58.93
Closed blocker, k_{bc}=0.1	0.465	13.60	188.9	5.890	73.66
Closed blocker, k_{bc}=1	0.422	13.69	205.7	5.231	53.08
Closed blocker, k_{bc}=10	0.428	12.80	203.2	5.014	47.15
Open blocker, k_{bo}=0.33, k_{ob}=0.32	0.484	13.04	187.5	4.724	48.34
Wild type	0.430	12.63	202.4	4.948	46.27
Mutant, no drug	0.743	9.64	131.7	2.419	18.90

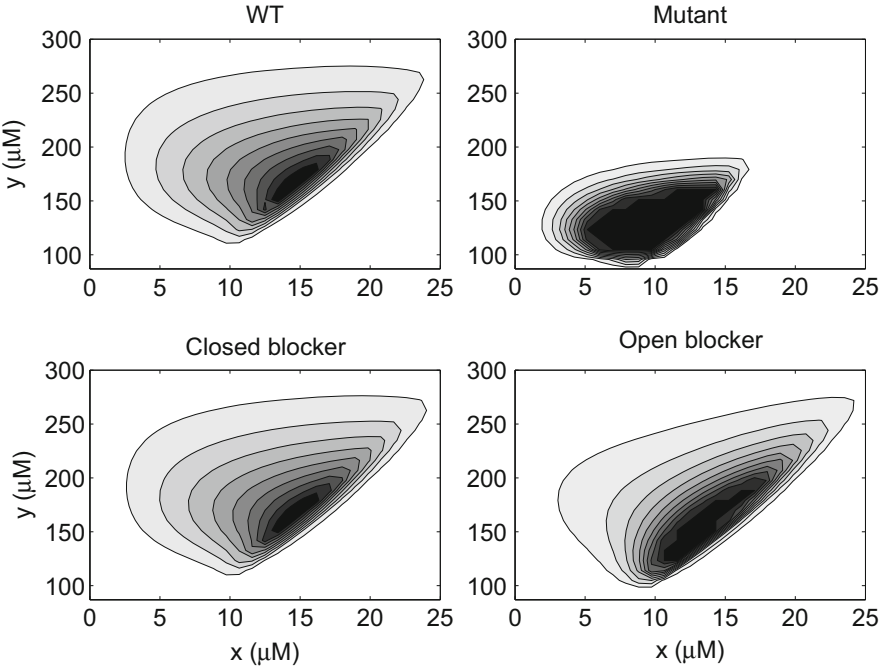

Fig. 6.6 Open probability density function for the wild type, the mutant ($\mu = 3$), the mutant plus the closed state blocker, and the mutant plus the open state blocker. We compute the stationary solution by solving the time-dependent equations until $T = 100$ ms. In the computation we use $\Delta t = 0.001$ ms, $\Delta x = 0.92$ μM, and $\Delta y = 9.3$ μM. The model parameters are specified in Table 6.1

6.5 Numerical Comparison of Optimal Open and Closed State Blockers

In the 1D case, we saw that for CO-mutations the closed state blocker was able to completely remove the effect of the mutation, whereas the open state blocker was less efficient. This result also holds in the 2D case. In Fig. 6.6, we compare the open probability density function of the steady state solution of the wild type

(solution of (6.1) and (6.2) with $\mu = 1$), the mutant (solution of (6.1) and (6.2) with $\mu = 3$), the optimal closed state blocker (solution of (6.5)–(6.7) using $\mu = 3$ and $k_{bc} = 10\ \text{ms}^{-1}$) and the optimal open state blocker (solution of (6.8)–(6.10) with $\mu = 3, k_{ob} = 0.3225\ \text{ms}^{-1}$, $k_{bo} = 0.3346\ \text{ms}^{-1}$). We observe that it is hard to see any difference between the open probability density function of the wild type and the mutant when the closed state blocker is applied. In addition, the optimal open state blocker improves the solution, but not as much as the closed state blocker does.

6.6 Stochastic Simulations in 2D Using Optimal Drugs

We have used the probability density approach to find an optimal closed state blocker. In Fig. 6.7 we show how the closed state blocker works in a dynamic

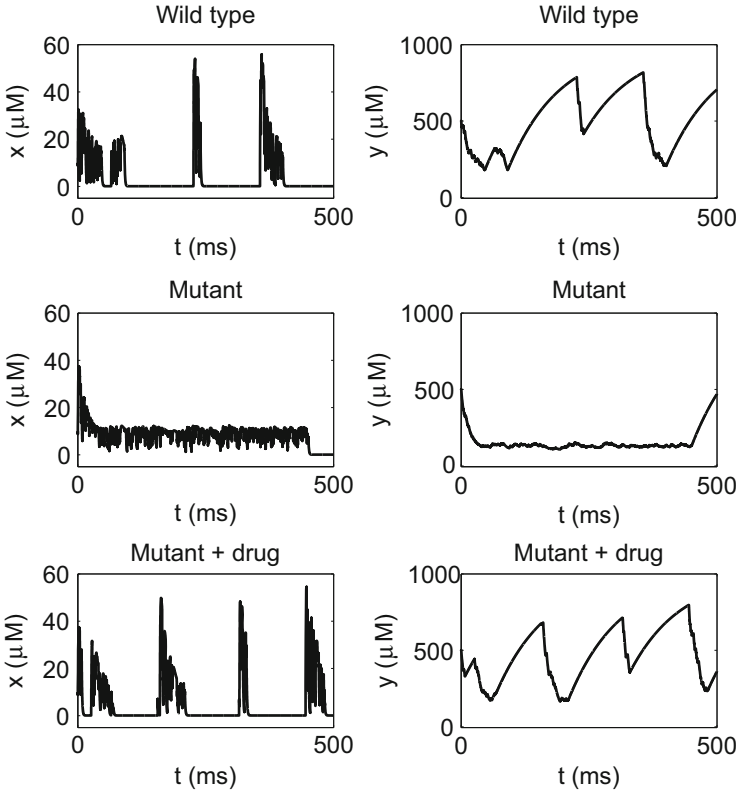

Fig. 6.7 Stochastic simulation of dyad concentrations (*left*, $x = x(t)$) and JSR concentrations (*right*, $y = y(t)$) for the wild type (*upper*), the mutant ($\mu = 3$, *middle*), and the mutant where the closed state drug is applied (*lower*, $k_{bc} = 10\ \text{ms}^{-1}$). Here we use $\Delta t = 0.01$ ms. The model parameters are specified in Table 6.1, and the initial conditions are given by $x(0) = c_0$ and $y(0) = c_1$ with the channel being closed

simulation based on the scheme (5.11) and (5.12). We plot the concentrations of the wild type, the mutant ($\mu = 3$), and the mutant when the closed state blocker is applied ($k_{bc} = 10\ \mathrm{ms}^{-1}$, $k_{cb} = (\mu - 1)k_{bc}$). The dyad concentrations ($x = x(t)$) are on the left-hand side and the JSR concentrations ($y = y(t)$) are on the right-hand side. As for the 1D simulations, we observe that the mutations significantly reduce the variability of the solutions and that this effect is basically completely repaired by the closed state blocker.

6.7 Notes

1. The 2D stochastic differential equation and the associated probability density system is taken from Huertas and Smith [35].