A Appendix

Exercises

A.1 Exercise 1

Show that the first quadrant $Q = \{u \geq 0, v \geq 0\}$ is invariant, i.e. orbits that begin in Q will always remain in Q.

A.2 Exercise 2

Show that Γ_u defined by equation 1.8 is an orbit, and (ii) that orbits cannot cross Γ_u.

A.3 Exercise 3

Show that the regions II and IV are invariant in that, if an orbit starts in II (or IV), then it must stay in II (or IV).

PK and PD models

A.4 The Kozielska PK

Kozielska et al., used a bolus dose and a sample drug PK model to simulate drug concentration dynamics in the plasma [24]. The PK model is for subcutaneous dosing with two compartments and is given by

$$\frac{dA_d}{dt} = -k_a A_d, \tag{A.1}$$

$$\frac{dA_c}{dt} = k_a A_d - \frac{CL}{V_1} A_c - \frac{CL_d}{V_1} A_c + \frac{CL_d}{V_2} A_p, \tag{A.2}$$

$$\frac{dA_p}{dt} = \frac{CL_d}{V_1} A_c - \frac{CL_d}{V_2} A_p, \tag{A.3}$$

where A_d denotes the amount in the depot compartment, A_c denotes the amount in the central compartment and A_p denotes the amount in the peripheral compartment. Table 1 gives the values and meaning of various parameters used by Kozielska et al., in the PK model [24].

A.5 The Stevens PK

$$\frac{dA_c}{dt} = -\left(\frac{CL_1}{V_1} + \frac{Q_1}{V_1} + \frac{Q_2}{V_1}\right) A_c + \frac{Q_1}{V_2} A_p + \frac{Q_2}{V_3} A_b, \tag{A.4}$$

$$\frac{dA_p}{dt} = -\frac{Q_1}{V_2}A_p + \frac{Q_1}{V_1}A_c, \tag{A.5}$$

$$\frac{dA_b}{dt} = -\left(\frac{CL_3}{V_3} + \frac{Q_2}{V_3}\right)A_b + \frac{Q_2}{V_3}A_b, \tag{A.6}$$

where A_c denotes the amount in the central compartment, A_p denotes the amount in the peripheral compartment and A_b denotes the amount in the brain compartment. Table 2 gives the values and meaning of various parameters used by Stevens et al., in the PK model [12].

A.6 The Stevens PD

The PD model equations are given by (2.5)-(2.6). The estimated parameter values which gave the best fit with the rat data are listed in Table 3.