Chapter 25

Medical Markov Chains

The progression of a medical condition is often considered as unpredictable. Although the risk factors are well known, for example for a heavy smoker, the onset of illness is not predictable. At the level of cell behaviour, the failure of functions can be random. Moreover, a chronic medical condition, cancer for example, can progress through stages of increasing severity.

Let us assume that a condition progresses as a continuous-time Markov chain.

25.1 Successive states

Suppose we consider *chronic kidney disease* with three states:
$X = 0$ mild
$X = 1$ medium
$X = 2$ severe

Let us take a model that the condition progresses according to a continuous-time Markov chain, through the states, $0 \longrightarrow 1 \longrightarrow 2$, and the progression (in the absence of treatment) is irreversible. We assume that the transition graph is given by (figure 25.1).

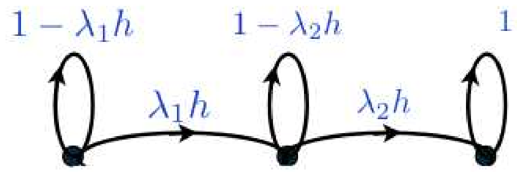

Figure 25.1: Transition graph for the progression of a stochastic chronic medical condition. The transition probabilities are shown for a short time h. Clearly, states 0 and 1 are transient, while state 2 is an absorbing state. Thus, in the long term, the system is certain to be in state 2.

That is, the transition matrix has the form:

$$\mathsf{P}(h) = \begin{pmatrix} 1-\lambda_1 h & \lambda_1 h & 0 \\ 0 & 1-\lambda_2 h & \lambda_2 h \\ 0 & 0 & 1 \end{pmatrix} \quad . \tag{25.1}$$

Then the corresponding jump-rate matrix will have the form:

$$\mathsf{Q} = \lim_{h\to 0}\left(\frac{\mathsf{P}(h)-\mathsf{I}}{h}\right) = \begin{pmatrix} -\lambda_1 & \lambda_1 & 0 \\ 0 & -\lambda_2 & \lambda_2 \\ 0 & 0 & 0 \end{pmatrix} \quad . \tag{25.2}$$

where λ_1, λ_2 describe the transition rates $0 \to 1$, $1 \to 2$. Again, the sum along each row must be zero.

Then the Kolmogorov forward equations are

$$\dot{\mathsf{P}} = \mathsf{P}\mathsf{Q} \quad . \tag{25.3}$$

That is, explicitly:

$$\begin{pmatrix} \dot{P}_{00} & \dot{P}_{01} & \dot{P}_{02} \\ \dot{P}_{10} & \dot{P}_{11} & \dot{P}_{12} \\ \dot{P}_{20} & \dot{P}_{21} & \dot{P}_{22} \end{pmatrix} = \begin{pmatrix} P_{00} & P_{01} & P_{02} \\ P_{10} & P_{11} & P_{12} \\ P_{20} & P_{21} & P_{22} \end{pmatrix} \begin{pmatrix} -\lambda_1 & \lambda_1 & 0 \\ 0 & -\lambda_2 & \lambda_2 \\ 0 & 0 & 0 \end{pmatrix} \quad . \tag{25.4}$$

with the formal solution:

$$\mathsf{P} = \exp(\mathsf{Q}t) \quad . \tag{25.5}$$

The calculation of the exponential of the matrix is complicated, so we will choose the direct solution of the Kolmogorov equations.

We are interested in the following question. If a patient begins in $X = 0$, what is the probability that the patient is in $X = 1$ or $X = 2$ at a later time ? To solve this problem, we must integrate the Kolmogorov equation, with the initial conditions that the patient is, with certainty in state 0 at $t = 0$. That is:

$$P_{00}(0) = 1 \quad , \quad P_{01}(0) = 0 \quad , \quad P_{02}(0) = 0 \quad . \tag{25.6}$$

and we week the values:

$$P_{00}(t) \quad , \quad P_{01}(t) \quad , \quad P_{02}(t) \quad . \tag{25.7}$$

Then the first row of $\dot{\mathsf{P}}$ gives:

$$\begin{aligned} \dot{P}_{00} &= P_{00}(-\lambda_1) \\ \dot{P}_{01} &= P_{00}(\lambda_1) + P_{01}(-\lambda_2) \\ \dot{P}_{02} &= P_{01}(\lambda_2) \end{aligned}$$

Note that if we add all three equations, the right-hand-side cancels out giving:

$$\dot{P}_{00} + \dot{P}_{01} + \dot{P}_{02} = 0$$

which is as we expect since: $P_{00} + P_{01} + P_{12} = 1$, then:

$$\frac{d}{dt}(P_{00} + P_{01} + P_{12}) = 0 \qquad .$$

These equations can be integrated directly and successively.

The first equation can be written as:

$$\frac{dP_{00}}{dt} = -\lambda_1 P_{00} \qquad , \quad \Rightarrow \qquad \frac{dP_{00}}{P_{00}} = -\lambda_1 dt \tag{25.8}$$

after integrating, this gives:

$$\ln P_{00} = -\lambda_1 t + A \tag{25.9}$$

where the constant, A, is found form the initial condition $P_{00}(0) = 1$, which implies $A = 0$. Then, this can be written:

$$\boxed{P_{00}(t) = e^{-\lambda_1 t}} \qquad . \tag{25.10}$$

Then the next equation to be solved is, substituting the solution for P_{00} :

$$\dot{P}_{01} = \lambda_1 e^{-\lambda_1 t} + P_{01}(-\lambda_2) \qquad . \tag{25.11}$$

That is:

$$\dot{P}_{01} + \lambda_2 P_{01} = \lambda_1 e^{-\lambda_1 t} \qquad . \tag{25.12}$$

To solve this differential equation, we use the *integrating factor* method.

This means multiplying across by the factor: $e^{\lambda_2 t}$ that gives,

$$e^{\lambda_2 t}\frac{d}{dt}P_{01} + \lambda_2 e^{\lambda_2 t}P_{01} = \lambda_1 e^{(\lambda_2-\lambda_1)t} \qquad . \tag{25.13}$$

which can be written as:

$$\frac{d}{dt}\left(e^{\lambda_2 t}P_{01}\right) = \lambda_1 e^{(\lambda_2-\lambda_1)t} \qquad . \tag{25.14}$$

and this integrates as follows:

$$e^{\lambda_2 t}P_{01} = \int \lambda_1 e^{(\lambda_2-\lambda_1)t}\ dt \tag{25.15}$$

giving, for $\lambda_1 \neq \lambda_2$,

$$e^{\lambda_2 t}P_{01} = \frac{\lambda_1}{\lambda_2 - \lambda_1}e^{(\lambda_2-\lambda_1)t} + B \tag{25.16}$$

with the initial conditions, we have

$$0 = \frac{\lambda_1}{\lambda_2 - \lambda_1} + B \tag{25.17}$$

which determines B. Then we use this result is equation (25.16) to give:

$$e^{\lambda_2 t}P_{01} = \frac{\lambda_1}{\lambda_2 - \lambda_1}\left(e^{(\lambda_2-\lambda_1)t} - 1\right) \qquad . \tag{25.18}$$

One further step of simplification leads to:

$$\boxed{P_{01}(t) = \frac{\lambda_1}{\lambda_2 - \lambda_1}\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right)} \quad , \qquad \lambda_1 \neq \lambda_2 \qquad . \tag{25.19}$$

When $\lambda_1 = \lambda_2 = \lambda$, then we can invoke L'Hôpital's rule to resolve the issue, giving us:

$$\boxed{P_{01}(t) = \lambda t e^{-\lambda t}} \quad \lambda_1 = \lambda_2 = \lambda \qquad . \tag{25.20}$$

Of course, it is simpler to get the result directly from (25.15), since this would give (when $\lambda_1 = \lambda_2$):

$$e^{\lambda t} P_{01} = \int \lambda \, dt = \lambda t \tag{25.21}$$

This almost completes the work since:

$$\boxed{P_{00}(t) + P_{01}(t) + P_{02}(t) = 1} \qquad \text{for all} \quad t \qquad . \tag{25.22}$$

Therefore:

$$P_{02}(t) = 1 - P_{00} - P_{01} = 1 - e^{-\lambda_1 t} - \frac{\lambda_1}{(\lambda_2 - \lambda_1)} \left(e^{-\lambda_1 t} - e^{-\lambda_2 t} \right) \qquad . \tag{25.23}$$

While, for $\lambda_1 = \lambda_2 = \lambda$, we get:

$$P_{02}(t) = 1 - e^{-\lambda t}(1 + \lambda t) \qquad . \tag{25.24}$$

Note that as $t \to +\infty$, $P_{02}(t) \to 1$ as expected. That is, since $X = 2$ is the absorbing state in this system, then eventually (in the long run) the system will finish in $X = 2$ with certainty.

25.2 Arrival times

From the equations above, the average time the patient spends in any one state, and the expected time to reach that state can be deduced.

25.2.1 Time in state 0

For the example, we have:

$$P_{00}(t) = e^{-\lambda_1 t} \qquad . \tag{25.25}$$

So letting T_0 be the continuous random variable that denotes the time spent in state $X = 0$, then: $P(T_0 \geq t)$ will be the probability that the patient is still in 0 after time t. Thus:

$$P(T_0 \geq t) = P_{00}(t) \qquad . \tag{25.26}$$

Then we have:

$$P(T_0 \leq t) = 1 - P_{00}(t) = 1 - e^{-\lambda_1 t} \tag{25.27}$$

with, the associated probability density:

$$f_{T_0}(t) = \lambda_1 e^{-\lambda_1 t} \qquad . \tag{25.28}$$

This is the familiar exponential density so that:

$$\mathbb{E}(T_0) = \frac{1}{\lambda_1} \qquad , \qquad \mathrm{var}(T_0) = \frac{1}{\lambda_1^2} \qquad . \tag{25.29}$$

This gives the expected time that the patient spends with a mild condition before it worsens.

25.2.2 Time in state 1

Suppose the initial state was $X(0) = 1$. That is the condition of the patient at the start of our observation as determined to be medium. Then the initial conditions would be:

$$P_{10}(0) = 0 \quad , \quad P_{11}(0) = 1 \quad , \quad P_{12}(0) = 0 \qquad . \tag{25.30}$$

In order to find the probabilities for the future condition: $P_{10}(t), P_{11}(t)$, and $P_{12}(t)$, we need to solve the Kolmogorov equations:

$$\frac{d}{dt}\mathsf{P} = \mathsf{PQ} \qquad . \tag{25.31}$$

In particular, along the second row:

$$\frac{d}{dt}P_{10} = -\lambda_1 P_{10} \tag{25.32}$$

$$\frac{d}{dt}P_{11} = \lambda_1 P_{10} - \lambda_2 P_{11} \tag{25.33}$$

$$\frac{d}{dt}P_{12} = \lambda_2 P_{11} \tag{25.34}$$

$$\tag{25.35}$$

Then the first equation gives:

$$P_{10}(t) = Ce^{-\lambda_1 t} \qquad . \tag{25.36}$$

Applying the initial condition gives: $C = 0$, so that: $P_{10}(t) = 0$. That is, there is zero probability of being in the mild condition if you start in the medium condition. This makes sense sicne this is a progressive condition.

The second equation is simple, since $P_{10}(t) = 0$, namely

$$\frac{d}{dt}P_{11} = -\lambda_2 P_{11} \tag{25.37}$$

which can be integrated, and with initial conditions applied gives:

$$P_{11}(t) = e^{-\lambda_2 t} \qquad . \tag{25.38}$$

It then follows that, since the probabilities must add to one:

$$P_{12}(t) = 1 - e^{-\lambda_2 t} \tag{25.39}$$

That is P_{11} and P_{12} are exponential variables. In particular, as in section 25.2.1, the expected time the patient spends in state 1 is:

$$\mathbb{E}\left(T_1\right) = \frac{1}{\lambda_2} \qquad . \tag{25.40}$$

25.2.3 Time to arrive in state 2

Having calculated the probabilities of being in each state, we can now calculate some parameters. Let T_2 be the arrival time for $X = 2$. That is T_2 is the time taken for the condition to progress from mild to severe. Then: $P_{02}(t) = P(T_2 \leq t) = F_{T_2}(t)$ is the (cumulative) probability distribution, and the density

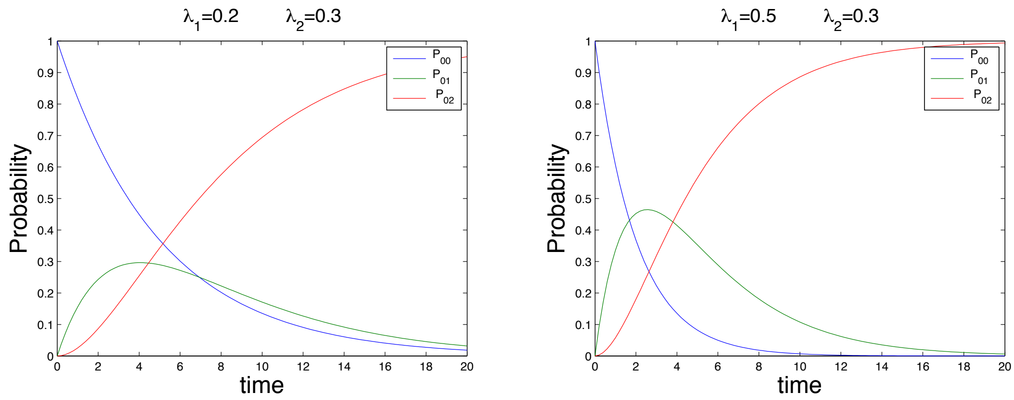

Figure 25.2: Probabilities for the continuous-time Markov chain described by the jump-rate matrix, equation (25.2). with the state initially in $X = 0$. The curves shown are for the rates: Left: $\lambda_1 = 0.2$,$\lambda_2 = 0.3$ (slow departure from $X = 0$). Right: $\lambda_1 = 0.5$,$\lambda_2 = 0.3$ (rapid departure from $X = 0$).
As indicated by the rising red line, at long times the probability of being in the absorbing state, $X = 2$, is certain.

is:

$$f_{T_2}(t) = \frac{d}{dt}F_{T_2}(t) = \frac{d}{dt}P_{02}(t) = \left(\frac{\lambda_1\lambda_2}{\lambda_2 - \lambda_1}\right)\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right) \qquad . \tag{25.41}$$

And:

$$\begin{aligned}
\mathbb{E}(T_2) &= \int_0^\infty t f_{T_2}(t)dt \\
\mathbb{E}(T_2) &= \int_0^\infty \left(\frac{\lambda_1\lambda_2}{\lambda_2 - \lambda_1}\right) \underset{\substack{\downarrow \\ u}}{t}\, \underbrace{\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right)}_{\frac{dv}{dt}} dt \\
&= \frac{\lambda_1\lambda_2}{(\lambda_2 - \lambda_1)}\left[-\frac{1}{\lambda_2^2} + \frac{1}{\lambda_1^2}\right] \\
\underset{\downarrow}{\mathbb{E}(T_2)} &= \frac{1}{\lambda_1} + \frac{1}{\lambda_2}
\end{aligned}$$

$$\begin{array}{ccccc}
\text{expected time} & = & \text{expected time} & + & \text{expected time} \\
0 \to 2 & & 0 \to 1 & & 1 \to 2
\end{array}$$

. . . as 'expected'.

This is not entirely unexpected since the processes are Markovian. The transitions, $0 \to 1$ and $1 \to 2$, (as for a Poisson process) occur in disjoint time intervals, and therefore are independent processes.

For example, if we had: $\lambda_1 = 0.05$ yr^{-1}; $\lambda_2 = 0.1$ yr^{-1}

$$\mathbb{E}(T_2) = 20 + 90 = 30 \text{ years.}$$

25.3 Parallel transitions

Suppose that the medical condition is such that there are 3 degrees of severity, as before, $X = 0, 1, 2$, but it is possible for the condition to progress directly from $X = 0$ to $X = 2$, as well as through $X = 1$.

Consider the jump-rate matrix to be:

$$\mathsf{Q} = \begin{pmatrix} -\lambda_1 - \lambda_2 & \lambda_1 & \lambda_2 \\ 0 & -\lambda_3 & \lambda_3 \\ 0 & 0 & 0 \end{pmatrix} \quad . \tag{25.42}$$

where λ_1, λ_2 and λ_3, describe the transition rates $0 \to 1$, $0 \to 2$, and $1 \to 2$.

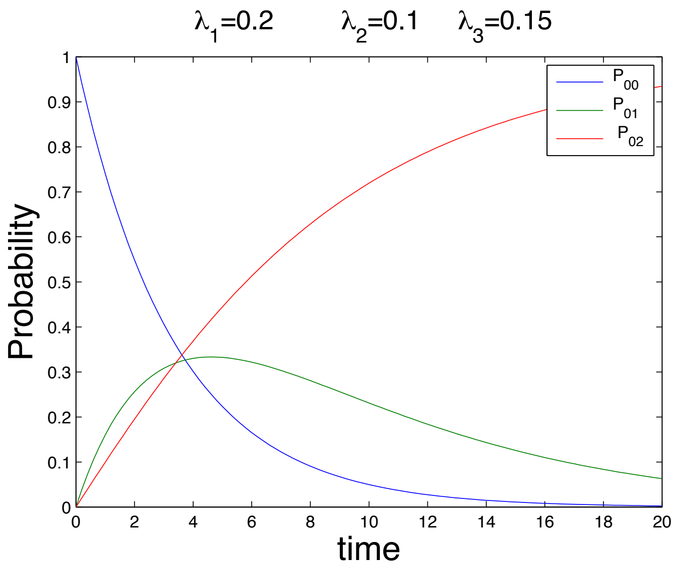

Figure 25.3: Probabilities for the continuous-time Markov chain described by the jump-rate matrix, equation (25.42). with the state initially in $X = 0$. The curves shown are for the rates: $\lambda_1 = 0.2$,$\lambda_2 = 0.1$, $\lambda_3 = 0.15$ As indicated by the rising red line, at long times, the probability of being in the absorbing state,$X = 2$, is certain.

Then the Kolmogorov forward equations are:

$$\begin{aligned} \dot{P}_{00} &= P_{00}(-\lambda_1 - \lambda_2) \\ \dot{P}_{01} &= P_{00}(\lambda_1) + P_{01}(-\lambda_3) \\ \dot{P}_{02} &= P_{00}(\lambda_2) + P_{01}(\lambda_3) \end{aligned}$$

The equations can be integrated in exactly the same manner as before, the first equation gives:

$$P_{00}(t) = e^{-(\lambda_1+\lambda_2)t} \quad . \tag{25.43}$$

The second equation requires some more work:

$$\frac{d}{dt}P_{01} + \lambda_3 P_{01} = \lambda_1 e^{-(\lambda_1+\lambda_2)t} \quad . \tag{25.44}$$

The integrating factor gives:

$$e^{\lambda_3 t}\frac{d}{dt}P_{01} + \lambda_3 e^{\lambda_3 t} P_{01} = \lambda_1 e^{(\lambda_3-\lambda_1-\lambda_2)t} \quad . \tag{25.45}$$

$$\frac{d}{dt}\left(e^{\lambda_3 t}P_{01}\right) = \lambda_1 e^{(\lambda_3-\lambda_1-\lambda_2)t} \qquad . \tag{25.46}$$

$$e^{\lambda_3 t}P_{01} = \frac{\lambda_1}{(\lambda_3-\lambda_1-\lambda_2)}e^{(\lambda_3-\lambda_1-\lambda_2)t} + A \qquad . \tag{25.47}$$

As before, at $t = 0$, there is zero probability that the patient is in state 2. Therefore

$$A = -\frac{\lambda_1}{(\lambda_3-\lambda_1-\lambda_2)} \qquad . \tag{25.48}$$

So that:

$$\boxed{P_{01}(t) = \frac{\lambda_1}{(\lambda_3-\lambda_1-\lambda_2)}\left(e^{-(\lambda_1+\lambda_2)t} - e^{-\lambda_3 t}\right)} \qquad . \tag{25.49}$$

And finally:

$$\boxed{P_{02}(t) = 1 - e^{-(\lambda_1+\lambda_2)t} - \frac{\lambda_1}{(\lambda_3-\lambda_1-\lambda_2)}\left(e^{-(\lambda_1+\lambda_2)t} - e^{-\lambda_3 t}\right)} \qquad . \tag{25.50}$$

In this case, the expected time that the patient stays in state 0 is:

$$\mathbb{E}\left(T_0\right) = \frac{1}{\lambda_1+\lambda_2} \qquad . \tag{25.51}$$

The expected arrival time in state 2, given that the patient starts in $X = 0$ is:

$$\mathbb{E}\left(T_2\right) = \int_0^\infty t\frac{d}{dt}P_{02}(t)dt \tag{25.52}$$

which, after some work and using the relation:

$$\int_0^\infty te^{-at}dt = \frac{1}{a^2}$$

leads to:

$$\mathbb{E}\left(T_2\right) = \frac{1}{\lambda_3} \times \left(\frac{\lambda_1+\lambda_3}{\lambda_1+\lambda_2}\right) \qquad . \tag{25.53}$$

25.4 Reversing the condition

Suppose that the progress of the condition can be reversed, so that there are transitions $2 \to 1$. In that case, state 0 is still transient, but the system is not certain to end up in $X = 2$.

An example of this is given by the transition graph in figure (25.4).

We take the jump-rate matrix to have the form:

$$\mathsf{Q} = \begin{pmatrix} -\lambda_1 & \lambda_1 & 0 \\ 0 & -\lambda_2 & \lambda_2 \\ 0 & \lambda_3 & -\lambda_3 \end{pmatrix} \qquad . \tag{25.54}$$

Then, starting in $X = 0$, the transitions take the pattern: $0 \to 1 \leftrightarrow 2$. An example of the results is shown in figure (25.5), where the probability of being in $X = 0$ decreases as before. However, there is soon an equilibrium in which the probability is divided between $X = 1$ and $X = 2$.

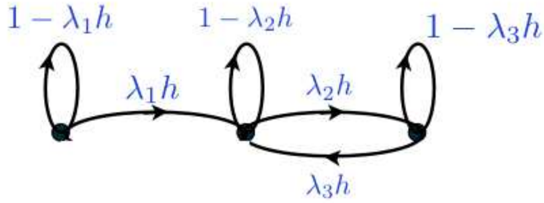

Figure 25.4: Transition graph for the progression of a stochastic chronic medical condition. The transition probabilities are shown for a short time h. In this case, we allow for a reversibility of the condtion, which is again stochastic, given by a transition from 2 to 1. Then, in the long run, 0 is transient, but states 1 and 2 are recurrent. An equilibrium will be created between states 1 and 2.

Of course, $X = 0$ is a transient state. However, we can obtain the equilibrium distribution

$$\begin{pmatrix}\pi_0 & \pi_1 & \pi_2\end{pmatrix}\begin{pmatrix}-\lambda_1 & \lambda_1 & 0 \\ 0 & -\lambda_2 & \lambda_2 \\ 0 & \lambda_3 & -\lambda_3\end{pmatrix} = \begin{pmatrix}0 & 0 & 0\end{pmatrix} \qquad . \tag{25.55}$$

This gives, multiplying the vector by the matrix, in the first column:

$$\pi_0 = 0$$

Then we have, for the third column:

$$\pi_1(-\lambda_2) + \pi_2\lambda_3 = 0 \qquad . \tag{25.56}$$

The same equation follows from the second column. In fact, this equation is exactly that which we would get from a consideration of detailed balance. That is, when in equilibrium the flow of probability between the states exactly cancel out so that a stationary state arises.

$$\pi_1 P_{12}(h) = \pi_2 P_{21}(h) \qquad . \tag{25.57}$$

that is:

$$\pi_1\lambda_2 h = \pi_2\lambda_3 h \qquad . \tag{25.58}$$

giving us,

$$\boxed{\pi_2 = (\lambda_2/\lambda_3)\pi_1} \qquad . \tag{25.59}$$

In addition to this we have the normalisation:

$$\pi_0 + \pi_1 + \pi_2 = 1 \tag{25.60}$$

This can be written as:

$$0 + \pi_1 + (\lambda_2/\lambda_3)\pi_1 = 1 \tag{25.61}$$

which gives:

$$\boxed{\pi_0 = 0 \qquad , \qquad \pi_1 = \frac{\lambda_3}{\lambda_2+\lambda_3} \qquad , \qquad \pi_2 = \frac{\lambda_2}{\lambda_2+\lambda_3}} \qquad . \tag{25.62}$$

So for the process shown in figure (25.5), with parameters: $\lambda_1 = 0.5$,$\lambda_2 = 0.5$, $\lambda_3 = 0.2$, we predict that equilibrium should result in the distribution:

$$\pi_0 = 0 \quad , \quad \pi_1 = \frac{0.2}{0.5+0.2} \approx 0.286 \quad , \quad \pi_2 = \frac{0.5}{0.5+0.2} \approx 0.714 \quad .$$

The numerical solution of the Kolmogorov equations, as shown in figure (25.5), is in complete agreement with this result, in the long run $t \to +\infty$.

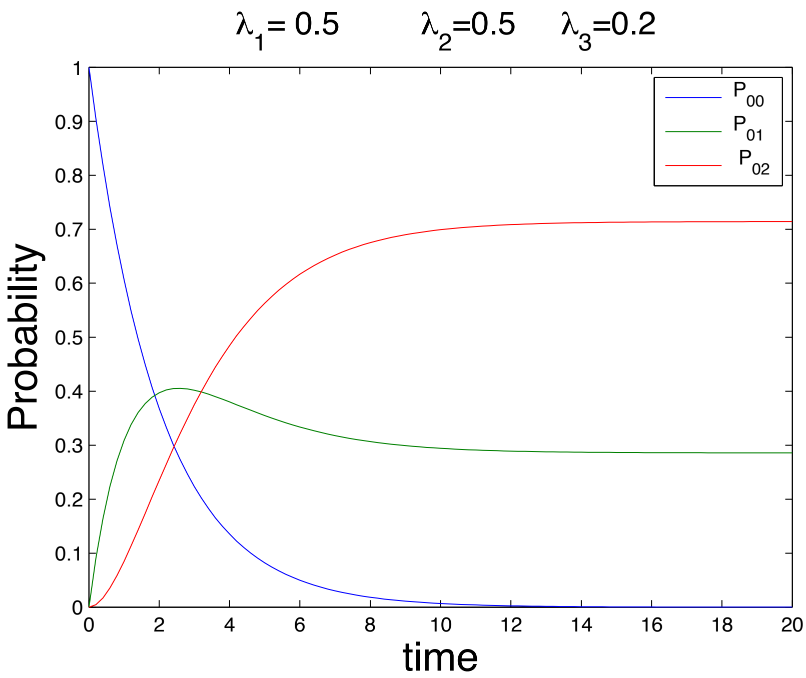

Figure 25.5: Probabilities for the continuous-time Markov chain described by the jump-rate matrix, equation (25.54). with the state initially in $X = 0$. The curves shown are for the rates: $\lambda_1 = 0.5$,$\lambda_2 = 0.5$, $\lambda_3 = 0.2$. The probability in the long-term is divided into an equilibrium between states $X = 1, 2$.

The exponential dependence of the probabilities derives from the jump-rate matrix. The exponent parameters are the eigenvalues of the jump-rate matrix.