A codimension-two bifurcation organises the dynamics of the transition between multipotent and fate-specified cell states

Nathan Schofield, Saeed Farjami, Andrea Rocco, Robert N. Kelsh, Jonathan H.P. Dawes

Supplementary Material

Appendix: Reduction to the normal form

This Appendix presents further details of the calculation outlined in section 3 in which we reduce the symmetric ODEs (3.1) - (3.3) to the normal form (3.12) shown in section 3(a). For completeness we recall these equations here. The general form of the ODEs in $\mathbb{R}^3$ is taken to be

$$\dot{x}_1 = g_1(x_1, x_2, x_3), \quad (1)$$
$$\dot{x}_2 = g_2(x_1, x_2, x_3) = g_1(x_2, x_3, x_1), \quad (2)$$
$$\dot{x}_3 = g_3(x_1, x_2, x_3) = g_1(x_3, x_1, x_2). \quad (3)$$

and the normal form at the double-zero bifurcation point is

$$\dot{z} = (p_1 + \mathrm{i}q_1)z + (p_2 + \mathrm{i}q_2)\bar{z}^2 + (p_3 + \mathrm{i}q_3)z|z|^2 \quad (4)$$

The calculation is divided into two parts: in section A.1 below we treat the linear and quadratic terms, and in section A.2 we focus on the cubic terms separately. The calculation is a centre manifold reduction in which we eliminate one variable and keep the remaining two (real) variables (y_2, y_3) which, after rescaling, introducing $(u_2, u_3) = (y_2, y_3/\sqrt{3})$ can be compactly written as the real and imaginary parts of a new complex variable $z \equiv u_2 + \mathrm{i}u_3$.

A.1 The linear and quadratic terms

In this section we consider just the linear and quadratic terms. Noting that $f(x_0, x_0, x_0) = 0$ we substitute the Taylor series (3.9) of $f(x_1, x_2, x_3)$ at the equilibrium point (x_0, x_0, x_0):

$$f(x_1, x_2, x_3) = f(x_0, x_0, x_0) + \eta_1 f_1 + \eta_2 f_2 + \eta_3 f_3 + Q(\eta_1, \eta_2, \eta_3) + C(\eta_1, \eta_2, \eta_3) \quad (5)$$

into (3.5) - (3.7), which are the ODEs for the linear combinations y_j:

$$\dot{y}_1 = \frac{1}{3}\Big[f(x_1, x_2, x_3) + f(x_2, x_3, x_1) + f(x_3, x_1, x_2)\Big] \quad (6)$$
$$\dot{y}_2 = \frac{1}{6}\Big[2f(x_1, x_2, x_3) - f(x_2, x_3, x_1) - f(x_3, x_1, x_2)\Big] \quad (7)$$
$$\dot{y}_3 = \frac{1}{2}\Big[f(x_3, x_1, x_2) - f(x_2, x_3, x_1)\Big]. \quad (8)$$

This yields

$$\begin{aligned}\dot{y}_1 &= \frac{1}{3}\Big[\eta_1 f_1 + \eta_2 f_2 + \eta_3 f_3 + \eta_2 f_1 + \eta_3 f_2 + \eta_1 f_3 + \eta_3 f_1 + \eta_1 f_2 + \eta_2 f_3 \\ &+\frac{1}{2}\eta_1^2 f_{11} + \frac{1}{2}\eta_2^2 f_{22} + \frac{1}{2}\eta_3^2 f_{33} + \eta_1\eta_2 f_{12} + \eta_2\eta_3 f_{23} + \eta_1\eta_3 f_{13} \\ &+\frac{1}{2}\eta_2^2 f_{11} + \frac{1}{2}\eta_3^2 f_{22} + \frac{1}{2}\eta_1^2 f_{33} + \eta_2\eta_3 f_{12} + \eta_1\eta_3 f_{23} + \eta_1\eta_2 f_{13} \\ &+\frac{1}{2}\eta_3^2 f_{11} + \frac{1}{2}\eta_1^2 f_{22} + \frac{1}{2}\eta_2^2 f_{33} + \eta_1\eta_3 f_{12} + \eta_1\eta_2 f_{23} + \eta_2\eta_3 f_{13}\Big], \qquad (9) \\ \dot{y}_2 &= \frac{1}{6}\Big[2\eta_1 f_1 + 2\eta_2 f_2 + 2\eta_3 f_3 - \eta_2 f_1 - \eta_3 f_2 - \eta_1 f_3 - \eta_3 f_1 - \eta_1 f_2 - \eta_2 f_3 \\ &+\eta_1^2 f_{11} + \eta_2^2 f_{22} + \eta_3^2 f_{33} + 2\eta_1\eta_2 f_{12} + 2\eta_2\eta_3 f_{23} + 2\eta_1\eta_3 f_{13} - \frac{1}{2}\eta_2^2 f_{11} - \frac{1}{2}\eta_3^2 f_{22} \\ &-\frac{1}{2}\eta_1^2 f_{33} - \eta_1\eta_3 f_{12} - \eta_1\eta_3 f_{23} - \eta_1\eta_2 f_{13} - \frac{1}{2}\eta_3^2 f_{11} - \frac{1}{2}\eta_1^2 f_{22} - \frac{1}{2}\eta_2^2 f_{33} \\ &-\eta_1\eta_3 f_{12} - \eta_1\eta_2 f_{23} - \eta_2\eta_3 f_{13}\Big], \qquad (10) \\ \dot{y}_3 &= \frac{1}{2}\Big[\eta_3 f_1 + \eta_1 f_2 + \eta_2 f_3 - \eta_2 f_1 - \eta_3 f_2 - \eta_1 f_3 + \frac{1}{2}\eta_3^2 f_{11} + \frac{1}{2}\eta_1^2 f_{22} + \frac{1}{2}\eta_2^2 f_{33} \\ &+\eta_1\eta_3 f_{12} + \eta_1\eta_2 f_{23} + \eta_2\eta_3 f_{13} - \frac{1}{2}\eta_2^2 f_{11} - \frac{1}{2}\eta_3^2 f_{22} - \frac{1}{2}\eta_1^2 f_{33} - \eta_2\eta_3 f_{23} - \eta_1\eta_2 f_{13}\Big]. \qquad (11)\end{aligned}$$

Equations (9) - (11) can be simplified by collecting like terms and substituting in for the η_i which are just linear combinations of the y_i. After tidying up we obtain, for the linear and quadratic terms

$$\begin{aligned}\dot{y}_1 &= \frac{1}{3}\Big[3y_1(f_1+f_2+f_3) + \frac{1}{2}(3y_1^2 + 6y_2^2 + 2y_3^2)(f_{11}+f_{22}+f_{33}) \\ &+(3y_1^2 - 3y_2^2 - y_3^2)(f_{12}+f_{23}+f_{13})\Big], \qquad (12) \\ \dot{y}_2 &= \frac{1}{6}\Big[6y_2 f_1 - 3(y_2+y_3)f_2 + 3(y_3-y_2)f_3 + (3y_2^2 + 6y_1y_2 - y_3^2)f_{11} \\ &+(3y_2y_3 - 3y_1y_3 - 3y_1y_2 - \frac{3}{2}y_2^2 + \frac{1}{2}y_3^2)f_{22} + (3y_1y_3 - 3y_1y_2 - 3y_2y_3 - \frac{3}{2}y_2^2 + \frac{1}{2}y_3^2)f_{33} \\ &+(6y_2^2 - 6y_1y_2 - 2y_3^2)f_{23} + (-3y_2^2 - 6y_2y_3 + 3y_1y_2 + y_3^2 - 3y_1y_3)f_{12} \\ &+(-3y_2^2 + 6y_2y_3 + 3y_1y_2 + y_3^2 + 3y_1y_3)f_{13}\Big], \qquad (13) \\ \dot{y}_3 &= \frac{1}{2}\Big[2y_3 f_1 + (3y_2 - y_3)f_2 - (y_3 + 3y_2)f_3 + 2(y_1y_3 - y_2y_3)f_{11} \\ &+(\frac{3}{2}y_2^2 + y_2y_3 + 3y_1y_2 - \frac{1}{2}y_3^2 - y_1y_3)f_{22} + (y_2y_3 - y_1y_3 - 3y_1y_2 - \frac{3}{2}y_2^2 + \frac{1}{2}y_3^2)f_{33} \\ &+(-3y_2^2 + 2y_2y_3 + 3y_1y_2 + y_3^2 + y_1y_3)f_{12} + (3y_2^2 + 2y_2y_3 - 3y_1y_2 - y_3^2 + y_1y_3)f_{13} \\ &-2(y_1y_3 + 2y_2y_3)f_{23}\Big]. \qquad (14)\end{aligned}$$

The linear term in (12) depends only on y_1, and has (by assumption) a negative coefficient: this is the eigenvalue $\lambda_1 \equiv f_1 + f_2 + f_3 < 0$. Hence the y_1 variable decays exponentially rapidly until this linear term is balanced by the largest nonlinear contribution. This relation implicitly defines the two-dimensional centre manifold which could more formally be expressed by writing y_1 as a function of y_2 and y_3 whose Taylor expansion could be computed order by order. Due to the simplicity of the linear terms, the leading order form of the centre manifold is given in this case by setting $\dot{y}_1 = 0$ in (12) and re-arranging this to solve for y_1. This yields the following:

$$y_1 = -\frac{(3y_2^2 + y_3^2)(f_{11} + f_{22} + f_{33} - f_{12} - f_{13} - f_{23})}{3(f_1 + f_2 + f_3)} + O(|y_2, y_3|^3) \qquad (15)$$

which indicates that, as expected, y_1 depends only quadratically on y_2 and y_3. Hence in order to compute the linear and quadratic terms in (13) and (14) we can omit any term that contains y_1. The leading order expression for y_1 also shows that the combination $3y_2^2 + y_3^2$ is relevant, and so a rescaling of one of these variables is required in order to tidy the algebra up as much as possible. We choose to rescale y_3 and introduce the new variables (u_2, u_3) defined by $(y_2, y_3) = (u_2, \sqrt{3}u_3)$ so that $(3y_2^2 + y_3^2)/3 = u_2^2 + u_3^2$.

In terms of the (u_2, u_3) variables we obtain

$$
\begin{aligned}
\dot{u}_2 &= u_2(f_1 - \frac{1}{2}f_2 - \frac{1}{2}f_3) + \frac{\sqrt{3}}{2}u_3(-f_2 + f_3) + u_2^2(\frac{1}{2}f_{11} - \frac{1}{2}f_{12} - \frac{1}{2}f_{13} - \frac{1}{4}f_{22} - \frac{1}{4}f_{33} + f_{23}) \\
&\quad + \frac{\sqrt{3}}{2}u_2u_3(-2f_{12} + 2f_{13} + f_{22} - f_{33}) + u_3^2(-\frac{1}{2}f_{11} + \frac{1}{2}f_{12} + \frac{1}{2}f_{13} + \frac{1}{4}f_{22} + \frac{1}{4}f_{33} - f_{23}) \\
\dot{u}_3 &= \frac{\sqrt{3}}{2}u_2(f_2 - f_3) + u_3(f_1 - \frac{1}{2}f_2 - \frac{1}{2}f_3) + \frac{\sqrt{3}}{4}u_2^2(f_{22} - 2f_{12} + 2f_{13} - f_{33}) \\
&\quad + \frac{1}{2}u_2u_3(-2f_{11} + f_{22} + f_{33} + 2f_{12} + 2f_{13} - 4f_{23}) + \frac{\sqrt{3}}{4}u_3^2(2f_{12} - 2f_{13} - f_{22} + f_{33})
\end{aligned}
$$

at which point the various combinations of partial derivatives are becoming more similar to each other. Indeed by writing the variables as a single complex variable $u_2 + \mathrm{i}u_3$, and defining the complex coefficient $p_2 + \mathrm{i}q_2$ by

$$
\begin{aligned}
p_2 &:= \frac{1}{2}(f_{11} - f_{12} - f_{13}) - \frac{1}{4}(f_{22} + f_{33}) + f_{23}\,, \\
q_2 &:= \frac{\sqrt{3}}{4}(f_{22} - f_{33} - 2f_{12} + 2f_{13})\,,
\end{aligned}
$$

we can write the (u_2, u_3) dynamics in the form

$$
\dot{u}_2 + \mathrm{i}\dot{u}_3 = \Big(f_1 - \frac{1}{2}f_2 - \frac{1}{2}f_3 + \mathrm{i}\frac{\sqrt{3}}{2}(f_2 - f_3)\Big)(u_2 + \mathrm{i}u_3) + (p_2 + \mathrm{i}q_2)(u_2 - \mathrm{i}u_3)^2\,,
$$

as anticipated from the symmetric bifurcation theory arguments presented in section 2(b), and from the form of (4). Hence the linear terms are also in the form expected from (4), with coefficients given by

$$
\begin{aligned}
p_1 &:= f_1 - \frac{1}{2}f_2 - \frac{1}{2}f_3\,, \\
q_1 &:= \frac{\sqrt{3}}{2}(f_2 - f_3)\,.
\end{aligned}
$$

A.2 The cubic terms

The procedure for obtaining the cubic terms is extremely similar. The major difference is that there are two sources of cubic terms: the first is the set of cubic terms in the Taylor series expansions for y_2 and y_3 themselves. The second is the set of quadratic terms already computed in (10) - (11) which contain a factor of y_1 which itself can be expressed as a combination of quadratic terms in y_2 and y_3; this is precisely (15). Combining these equations generates additional cubic terms in the dynamical equations for y_2 and y_3.

First, we turn to the cubic terms that appear directly in the Taylor series computation. From the expression $C(x_1,x_2,x_3)$ we obtain the cubic terms in the $\dot{y}_2$ and $\dot{y}_3$ equations to be:

$$\begin{aligned}
\dot{y}_2 &= \frac{1}{6}\Big[\frac{\eta_1^3}{3}f_{111}+\frac{\eta_2^3}{3}f_{222}+\frac{\eta_3^3}{3}f_{333}+\eta_1\eta_2^2f_{122}+\eta_2\eta_3^2f_{233}+\eta_3\eta_1^2f_{311}+\eta_1\eta_3^2f_{133}+\eta_2\eta_1^2f_{112}\\
&\quad+\eta_3\eta_2^2f_{223}+\underline{2\eta_1\eta_2\eta_3f_{123}}-\frac{\eta_2^3}{6}f_{111}-\frac{\eta_3^3}{6}f_{222}-\frac{\eta_1^3}{6}f_{333}-\frac{\eta_2\eta_3^2}{2}f_{122}-\frac{\eta_3\eta_1^2}{2}f_{233}\\
&\quad-\frac{\eta_1\eta_2^2}{2}f_{311}-\frac{\eta_2\eta_1^2}{2}f_{133}-\frac{\eta_3\eta_2^2}{2}f_{112}-\frac{\eta_1\eta_3^2}{2}f_{223}\underline{-\eta_1\eta_2\eta_3f_{123}}-\frac{\eta_3^3}{6}f_{111}-\frac{\eta_1^3}{6}f_{222}\\
&\quad-\frac{\eta_2^3}{6}f_{333}-\frac{\eta_3\eta_1^2}{2}f_{122}-\frac{\eta_1\eta_2^2}{2}f_{233}\\
&\quad-\frac{\eta_2\eta_3^2}{2}f_{311}-\frac{\eta_3\eta_2^2}{2}f_{133}-\frac{\eta_1\eta_3^2}{2}f_{112}-\frac{\eta_2\eta_1^2}{2}f_{223}\underline{-\eta_1\eta_2\eta_3f_{123}}\Big],\\
\dot{y}_3 &= \frac{1}{2}\Big[\frac{\eta_3^3}{6}f_{111}+\frac{\eta_1^3}{6}f_{222}+\frac{\eta_2^3}{6}f_{333}+\frac{\eta_3\eta_1^2}{2}f_{233}+\frac{\eta_2\eta_3^2}{2}f_{311}+\frac{\eta_3\eta_2^2}{2}f_{133}+\frac{\eta_1\eta_3^2}{2}f_{112}\\
&\quad+\frac{\eta_2\eta_1^2}{2}f_{223}+\underline{\eta_1\eta_2\eta_3f_{123}}-\frac{\eta_2^3}{6}f_{111}-\frac{\eta_3^3}{6}f_{222}-\frac{\eta_1^3}{6}f_{333}-\frac{\eta_2\eta_3^2}{2}f_{122}-\frac{\eta_3\eta_1^2}{2}f_{233}\\
&\quad-\frac{\eta_1\eta_2^2}{2}f_{311}-\frac{\eta_2\eta_1^2}{2}f_{133}-\frac{\eta_3\eta_2^2}{2}f_{112}-\frac{\eta_1\eta_3^2}{2}f_{223}\underline{-\eta_1\eta_2\eta_3f_{123}}\Big],
\end{aligned}$$

where the underlined terms cancel immediately, for any functional form of $f(x_1,x_2,x_3)$).

Since, as observed previously, $y_1=O(|y_2,y_3|^2)$, in order to deduce the cubic terms it is sufficient to ignore the y_1 terms in $\eta_1,\ldots,\eta_3$ and hence replace the components of $\boldsymbol{\eta}$ by $(\eta_1,\eta_2,\eta_3)=(2y_2,-(y_2+y_3),-y_2+y_3)$. After some further tidying up this results in the much simpler-looking versions:

$$\begin{aligned}
\dot{y}_2 &= \alpha_3y_2\left(y_2^2+\frac{y_3^2}{3}\right)+\beta_3y_3\left(y_2^2+\frac{y_3^2}{3}\right),\\
\dot{y}_3 &= \alpha_3y_3\left(y_2^2+\frac{y_3^2}{3}\right)+3\beta_3y_2\left(y_2^2+\frac{y_3^2}{3}\right),
\end{aligned}$$

where the coefficients are

$$\begin{aligned}
\alpha_3 &:= \frac{1}{4}\left(2f_{111}-3f_{112}+3f_{122}+3f_{133}-f_{222}-3f_{311}-f_{333}\right),\\
\beta_3 &:= \frac{1}{4}\left(f_{122}-f_{112}-f_{133}-f_{222}+2f_{223}-2f_{233}+f_{311}+f_{333}\right).
\end{aligned}$$

As before, moving to the rescaled variables $(y_2,y_3)=(u_2,\sqrt{3}u_3)$ allows us to write the pair of equations together in the complex form

$$\dot{u}_2+\mathrm{i}\dot{u}_3 = (\alpha_3-\mathrm{i}\sqrt{3}\beta_3)(u_2+\mathrm{i}u_3)(u_2^2+u_3^2). \tag{16}$$

Finally we turn to the cubic terms in y_2 and y_3 that emerge from quadratic terms which involve a single factor of y_1. Since this factor of y_1 corresponds, at leading order, to quadratic combinations of y_2 and y_3, via (15), these terms hence produce third order terms in y_2 and y_3. Extracting these terms from (13) and (14) we obtain

$$\begin{aligned}
\dot{y}_2 &= \frac{1}{6}\Big[(-3y_1y_3-3y_1y_2)f_{22}+3y_1(y_3-y_2)f_{33}-6y_1y_2f_{23}+6y_1y_2f_{11}\\
&\quad+3y_1(y_2-y_3)f_{12}+3y_1(y_2+y_3)f_{13}\Big],\\
\dot{y}_3 &= \frac{1}{2}\Big[y_1(3y_2-y_3)f_{22}-(y_1y_3+3y_1y_2)f_{33}-2y_1y_3f_{23}+2y_1y_3f_{11}+y_1(3y_2+y_3)f_{12}\\
&\quad+y_1(-3y_2+y_3)f_{13}\Big],
\end{aligned}$$

which simplifies, on collecting terms, to

$$\begin{aligned}
\dot{y}_2 &= \alpha_4 \hat{y}_1 y_2 + \beta_4 \hat{y}_1 y_3\,, \\
\dot{y}_3 &= \alpha_4 \hat{y}_1 y_3 - 3\beta_4 \hat{y}_1 y_2\,,
\end{aligned}$$

where

$$\begin{aligned}
\alpha_4 &:= \frac{1}{2}\left(2f_{11} + f_{12} + f_{13} - f_{22} - f_{33} - 2f_{23}\right)\,, \\
\beta_4 &:= \frac{1}{2}\left(f_{13} - f_{12} - f_{22} + f_{33}\right)\,,
\end{aligned}$$

and where $\hat{y}_1$ denotes the leading order term shown in (15). Hence when written in the rescaled variables these terms become:

$$\dot{u}_2 + \mathrm{i}\dot{u}_3 = (\alpha_4 - \mathrm{i}\sqrt{3}\beta_4)\hat{y}_1(u_2 + \mathrm{i}u_3)\,.$$

Combining these results, for the cubic terms we have the terms

$$\dot{u}_2 + \mathrm{i}\dot{u}_3 = -(\alpha_4 - \mathrm{i}\sqrt{3}\beta_4)\frac{(f_{11} + f_{22} + f_{33} - f_{12} - f_{13} - f_{23})}{(f_1 + f_2 + f_3)}(u_2 + \mathrm{i}u_3)(u_2^2 + u_3^2)\,, \tag{17}$$

where p_3 and q_3 are defined by combining the coefficients from (16) and (17) and are given in full in (3.17) and (3.18).