Supplementary material for "Modelling The Dynamics Of Phase Separation In Amorphous Solid Dispersions"

Appendix A. Linearization and stability analysis

In the main body of the paper, we derived conditions for stability of a solid dispersion based on the bulk free energy. Here we indicate how the interfacial energy may be incorporated in the analysis. We begin by recalling that the initial boundary value problem developed in the paper for the mole fraction of the drug X_d in the solid dispersion. This is given by:

$$\begin{aligned}
&\frac{\partial X_d}{\partial t} = \nabla \cdot \left\{ D_{\text{eff}}(X_d)\nabla X_d - D_d\delta_d^2 X_d \nabla\left(\nabla^2 X_d\right)\right\} \qquad \text{in} \qquad \Omega,\\
&\nabla X_d \cdot \mathbf{n} = 0, \qquad \nabla(\nabla^2 X_d)\cdot \mathbf{n} = 0 \qquad \text{on} \qquad \partial\Omega, \\
&X_d(x,y,t=0) = X_d^0(x,y) \qquad \text{for} \qquad (x,y)\in\Omega,
\end{aligned} \tag{1}$$

where Ω is the square region $\{(x,y)|0 < x, y < L\}$.

When manufacturing solid dispersions, the initial drug loading in the polymer is approximately uniform, so that we can write

$$X_d^0(x,y) = X_a + R(x,y) \tag{2}$$

where X_a is a constant and $R(x,y) \ll X_a$ is some small noisy perturbtion of X_a. In view of (2), we write

$$X_d(x,y,t) = X_a + \hat{X}(x,y,t), \tag{3}$$

where $\hat{X}(x,y,t)$ is a small perturbation about X_a. *If we find that $\hat{X} \to 0$ as $t \to \infty$, we conclude that the solid dispersion is stable. The solid dispersion is unstable if $\hat{X}$ grows in time.*

Substituting (3) into (1) and neglecting quadratic terms in $\hat{X}$, we obtain the linear problem

$$\begin{aligned}
&\frac{\partial \hat{X}}{\partial t} = D_{\text{eff}}(X_a)\left(\frac{\partial^2 \hat{X}}{\partial x^2} + \frac{\partial^2 \hat{X}}{\partial y^2}\right) - D_d\delta_d^2 X_a\left(\frac{\partial^4 \hat{X}}{\partial x^4} + \frac{\partial^4 \hat{X}}{\partial y^4} + 2\frac{\partial^4 \hat{X}}{\partial x^2 \partial y^2}\right) \quad \text{in} \quad 0 < x, y < L,\\
&\frac{\partial \hat{X}}{\partial x} = 0, \quad \frac{\partial^3 \hat{X}}{\partial x^3} = 0 \quad \text{on} \quad x = 0, L \quad \text{for} \quad 0 < y < L,\\
&\frac{\partial \hat{X}}{\partial y} = 0, \quad \frac{\partial^3 \hat{X}}{\partial y^3} = 0 \quad \text{on} \quad y = 0, L \quad \text{for} \quad 0 < x < L,\\
&\hat{X}(x,y,t=0) = R(x,y) \quad \text{for} \quad 0 < x, y < L.
\end{aligned} \tag{4}$$

This linear problem that can be solved using the method of separation of variables, and we find that

$$\begin{aligned}
\hat{X}(x,y,t) = X_a &+ \sum_{M=1}^{\infty} c_{M0} e^{-\lambda_{M0}t}\cos\left(\frac{M\pi x}{L}\right) + \sum_{N=1}^{\infty} c_{0N} e^{-\lambda_{0N}t}\cos\left(\frac{N\pi y}{L}\right)\\
&+ \sum_{M,N=1}^{\infty} c_{MN} e^{-\lambda_{MN}t}\cos\left(\frac{M\pi x}{L}\right)\cos\left(\frac{N\pi y}{L}\right)
\end{aligned} \tag{5}$$

where

$$\lambda_{MN} = \frac{(M^2+N^2)\pi^2}{L^2}\left(D_{\text{eff}}(X_a) + D_d X_a \delta_d^2 \frac{(M^2+N^2)\pi^2}{L^2}\right) \qquad \text{for} \quad M, N = 0, 1, 2, 3, ... \tag{6}$$

and where the c_{MN} are Fourier cosine coefficients. For the special case in which the initial data depends only on x, so that $\hat{X}(x,y,t=0) = R(x)$, the solution takes the one-dimensional form

$$\hat{X}(x,t) = X_a + \sum_{M=1}^{\infty} c_M e^{-\lambda_M t} \cos\left(\frac{M\pi x}{L}\right), \tag{7}$$

where

$$\lambda_M = \frac{M^2\pi^2}{L^2}\left(D_{\text{eff}}(X_a) + D_d X_a \delta_d^2 \frac{M^2\pi^2}{L^2}\right) \quad \text{for} \quad M = 1, 2, 3, ... \tag{8}$$

and where the c_M are Fourier cosine coefficients.

We now note that solid dispersion is stable if the λ's appearing in (5) or (7) are all positive. This will clearly be the case if $\lambda_{10} = \lambda_{01} = \lambda_1 > 0$, and this implies that

$$D_{\text{eff}}(X_a) > -D_d X_a \delta_d^2 \frac{\pi^2}{L^2}. \tag{9}$$

Notice that this expression includes the interfacial energy term δ_d^2. Setting $\delta_d = 0$ we recover $D_{\text{eff}}(X_a) > 0$, which is equivalent to $d^2 g_b/dX_d^2 > 0$ at $X_d = X_a$, and this is the classical thermodynamic criterion for stability discussed in Section 2.4 of the main body of the paper. We can re-write (9) as

$$2\chi_{dp} m^2 X_a(1 - X_a) < X_a \delta_d^2 \frac{\pi^2}{L^2}(m - (m-1)X_a)^3 + (m - (m-1)X_a)(m^2 - (m^2 - 1)X_a). \tag{10}$$

This last equation gives the criterion for solid dispersion stability in terms of the key model parameters.

Pattern formation

However, $D_{\text{eff}}(X_a)$ can be negative, and so some of the λ's can also be negative. For such cases, X_a is clearly an unstable steady state. The first mode only in the one-dimensional solution (7) is driven unstable if we choose $D_{\text{eff}}(X_a)$ such that $\lambda_1 < 0 < \lambda_2 < \lambda_3 < \lambda_4 < ......$ This is achieved by choosing $D_{\text{eff}}(X_a)$ so that (see (8))

$$D_{\text{eff}}(X_a) + D_d X_a \delta_d^2 \frac{\pi^2}{L^2} < 0 \quad \text{and} \quad D_{\text{eff}}(X_a) + 4D_d X_a \delta_d^2 \frac{\pi^2}{L^2} > 0$$

which implies

$$-4D_d X_a \delta_d^2 \frac{\pi^2}{L^2} < D_{\text{eff}}(X_a) < -D_d X_a \delta^2 \frac{\pi^2}{L^2}. \tag{11}$$

For a given X_a and m, it is possible to select a $D_{\text{eff}}(X_a)$ satisfying (11) by making an appropriate choice for χ_{dp}. In summary then, if we solve the fully nonlinear initial boundary value problem (1) subject to an initial condition of the form $X(x,y,t=0) = X_a + R(x)$ with $R(x)$ a noisy one-dimensional perturbation about X_a, then there will be an initial time period when the mode $\cos(\pi x/L)$ dominates. This will manifest itself as a single black stripe adjacent to a single white stripe if we colour regions where $X_d > X_a$ black, and regions where $X_d < X_a$ white.

Similarly, the first two modes of the one-dimensional solution are driven unstable for the choice

$$-9D_d X_a \delta_d^2 \frac{\pi^2}{L^2} < D_{\text{eff}}(X_a) < -4D_d X_a \delta_d^2 \frac{\pi^2}{L^2}. \tag{12}$$

In this case, the λ_2 and λ_1 modes emerge in the solution. The λ_2 mode will dominate if $-\lambda_2 > -\lambda_1$. Hence, in this case, there will be an initial time period when the shape $\cos(2\pi x/L)$ dominates, and this will manifest itself as either a black-white-black or white-black-white striped pattern if we plot regions where $X_d > X_a$ black, and regions where $X_d < X_a$ white.

The discussion for the fully two-dimensional case is similar. For example, for initial data of the form $X(x,y,t=0) = X_a + R(x,y)$ with $R(x,y)$ a noisy perturbation about X_a, then the λ_{11} mode is driven unstable if

$$-4D_d X_a \delta_d^2 \frac{\pi^2}{L^2} < D_{\text{eff}}(X_a) < -2D_d X_a \delta_d^2 \frac{\pi^2}{L^2}. \tag{13}$$

Hence, as the solution evolves and if λ_{11} is dominant, the mode $\cos(\pi x/L)\cos(\pi y/L)$ emerges, and this manifests itself as a two by two black and white chequered pattern using the colouring scheme described above.