Appendix 1 - Mathematical Modeling Parameters

We model the retinoic acid (RA) signaling system in the zebrafish hindbrain with chemical reactions, assuming diffusion of extracellular RA. A one-dimensional domain represents the anterior-posterior (A-P) axis of the hindbrain. The concentration of extracellular RA is represented by $[RA]_{out}$, intracellular RA by $[RA]_{in}$, binding proteins (Crabps) by $[BP]$, RA receptors by $[R]$, the RA degradation enzyme Cyp26a1 by $[Cyp]$, and Fgf by $[fgf]$. There are also two complexes that can form, $[RA-R]$ and $[RA-BP]$. The strength of the RA signal is represented by $[RA-R]^n$. We let *n=2* assuming co-operativity in signaling (White et al. 2007). The RA signal $[RA-R]$ is formed when $[RA]_{in}$ binds to $[R]$ or when $[RA-BP]$ binds to receptors $[R]$. We assume that $[RA-BP-R]$ is at quasi-equilibrium and is short-lived which simplifies the reaction

$$[RA-BP]+[R] \underset{\alpha_{off}}{\overset{\alpha_{on}}{\rightleftharpoons}} [RA-BP-R] \underset{\beta_{on}}{\overset{\beta_{off}}{\rightleftharpoons}} [RA-R]+[BP]$$

to

$$[RA-BP]+[R] \underset{j_{\beta}}{\overset{j_{\alpha}}{\rightleftharpoons}} [RA-R]+[BP]$$

where

$$j_{\alpha} = \frac{\beta_{off}\alpha_{on}}{\alpha_{off}+\beta_{off}}$$

and

$$j_{\beta} = \frac{\beta_{on}\alpha_{off}}{\alpha_{off}+\beta_{off}},$$

in the model. Molecules can degrade in both bound and unbound forms, with possibly different rates. For example, the complex $[RA-BP]$ may undergo either [RA] degradation or [BP] degradation. The $[RA-R]$ complex may only undergo $[R]$ degradation because the receptors are located inside the nucleus and we assume that RA can only be degraded outside the nucleus through interacting with [Cyp].

In the domain $0 \le X \le x_f$, we let

$$\begin{aligned}
&\frac{\partial [RA]_{out}}{\partial T} = D\frac{\partial^2 [RA]_{out}}{\partial X^2} + V(x) - (1+\beta)k_p[RA]_{out} + k_p[RA]_{in},\\
&\frac{\partial [RA]_{in}}{\partial T} = k_p[RA]_{out} + r_{\deg 2}[RA-R] + bp_{\deg 2}[RA-BP] - [CYP]_{RA}[RA]_{in} - k_p[RA]_{in}\\
&-r_{on}[RA]_{in}[R] + r_{off}[RA-R] - m_{on}[RA]_{in}[BP] + m_{off}[RA-BP],\\
&\frac{\partial [R]}{\partial T} = V_R - r_{\deg 1}[R] - r_{on}[RA]_{in}[R] + r_{off}[RA-R] - j_\alpha[RA-BP][R] + j_\beta[BP][RA-R],\\
&\frac{\partial [RA-R]}{\partial T} = r_{on}[RA]_{in}[R] - r_{off}[RA-R] + j_\alpha[RA-BP][R] - j_\beta[BP][RA-R] - r_{\deg 2}[RA-R],\\
&\frac{\partial [BP]}{\partial T} = V_{BP} - bp_{\deg 1}[BP] + [CYP]_{RABP}[RA-BP]\\
&-m_{on}[RA]_{in}[BP] + m_{off}[RA-BP] + j_\alpha[RA-BP][R] - j_\beta[BP][RA-R],\\
&\frac{\partial [RA-BP]}{\partial T} = -[CYP]_{RABP}[RA-BP] + m_{on}[RA]_{in}[BP] - m_{off}[RA-BP]\\
&-j_\alpha[RA-BP][R] + j_\beta[BP][RA-R] - bp_{\deg 2}[RA-BP], \qquad (0.1)
\end{aligned}$$

where

$$[Fgf] = f_0 \exp(-\lambda(X - x_f))$$

and

$$[CYP]_j = C_0 \begin{cases} \left(\dfrac{RA_{signal}}{RA_{signal} + \gamma^n(\delta + [Fgf])}\right), & 0 < X < x_f - 40, \\ 1, & X > x_f - 40, \end{cases}$$

with the coefficient $C_0 = ra_{\deg}$, for $j = RA$, and $C_0 = rabp_{\deg}$, for $j = RABP$.

A smaller region of interest than that of (White et al. 2007) is used, with X=0 corresponding to the posterior border of the anterior domain of high *cyp26a1* expression. The source of RA is posterior to the hindbrain so we let $V(X) = V_{RA}$ at $X > x_f - 40$, and $V(X) = 0$ otherwise. The anterior region has a no flux boundary condition

$$\frac{\partial [RA]_{out}}{\partial X} = 0 \text{ at } X = 0$$

and the posterior region has a leaky boundary condition

$$\frac{\partial [RA]_{out}}{\partial X} = -k_p [RA]_{out} \text{ at } X = x_f .$$