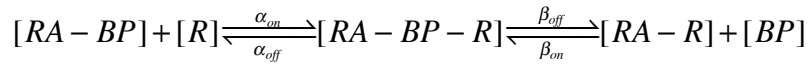
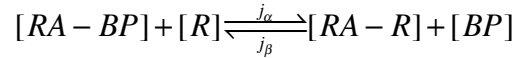


Appendix 1 - Mathematical Modeling Parameters

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



to



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 $0 \leq X \leq x_f$, we let

$$\begin{aligned}
\frac{\partial[RA]_{out}}{\partial T} &= D \frac{\partial^2[RA]_{out}}{\partial X^2} + V(x) - (1 + \beta)k_p[RA]_{out} + k_p[RA]_{in}, \\
\frac{\partial[RA]_{in}}{\partial T} &= k_p[RA]_{out} + r_{deg2}[RA - R] + bp_{deg2}[RA - BP] - [CYP]_{RA}[RA]_{in} - k_p[RA]_{in} \\
&\quad - r_{on}[RA]_{in}[R] + r_{off}[RA - R] - m_{on}[RA]_{in}[BP] + m_{off}[RA - BP], \\
\frac{\partial[R]}{\partial T} &= V_R - r_{deg1}[R] - r_{on}[RA]_{in}[R] + r_{off}[RA - R] - j_\alpha[RA - BP][R] + j_\beta[BP][RA - R], \\
\frac{\partial[RA - R]}{\partial T} &= r_{on}[RA]_{in}[R] - r_{off}[RA - R] + j_\alpha[RA - BP][R] - j_\beta[BP][RA - R] - r_{deg2}[RA - R], \\
\frac{\partial[BP]}{\partial T} &= V_{BP} - bp_{deg1}[BP] + [CYP]_{RABP}[RA - BP] \\
&\quad - m_{on}[RA]_{in}[BP] + m_{off}[RA - BP] + j_\alpha[RA - BP][R] - j_\beta[BP][RA - R], \\
\frac{\partial[RA - BP]}{\partial T} &= -[CYP]_{RABP}[RA - BP] + m_{on}[RA]_{in}[BP] - m_{off}[RA - BP] \\
&\quad - j_\alpha[RA - BP][R] + j_\beta[BP][RA - R] - bp_{deg2}[RA - BP], \tag{0.1}
\end{aligned}$$

where

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

and

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

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

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