Independent Mean/Variance Regulation in the Self-Enhanced Degradation Motif

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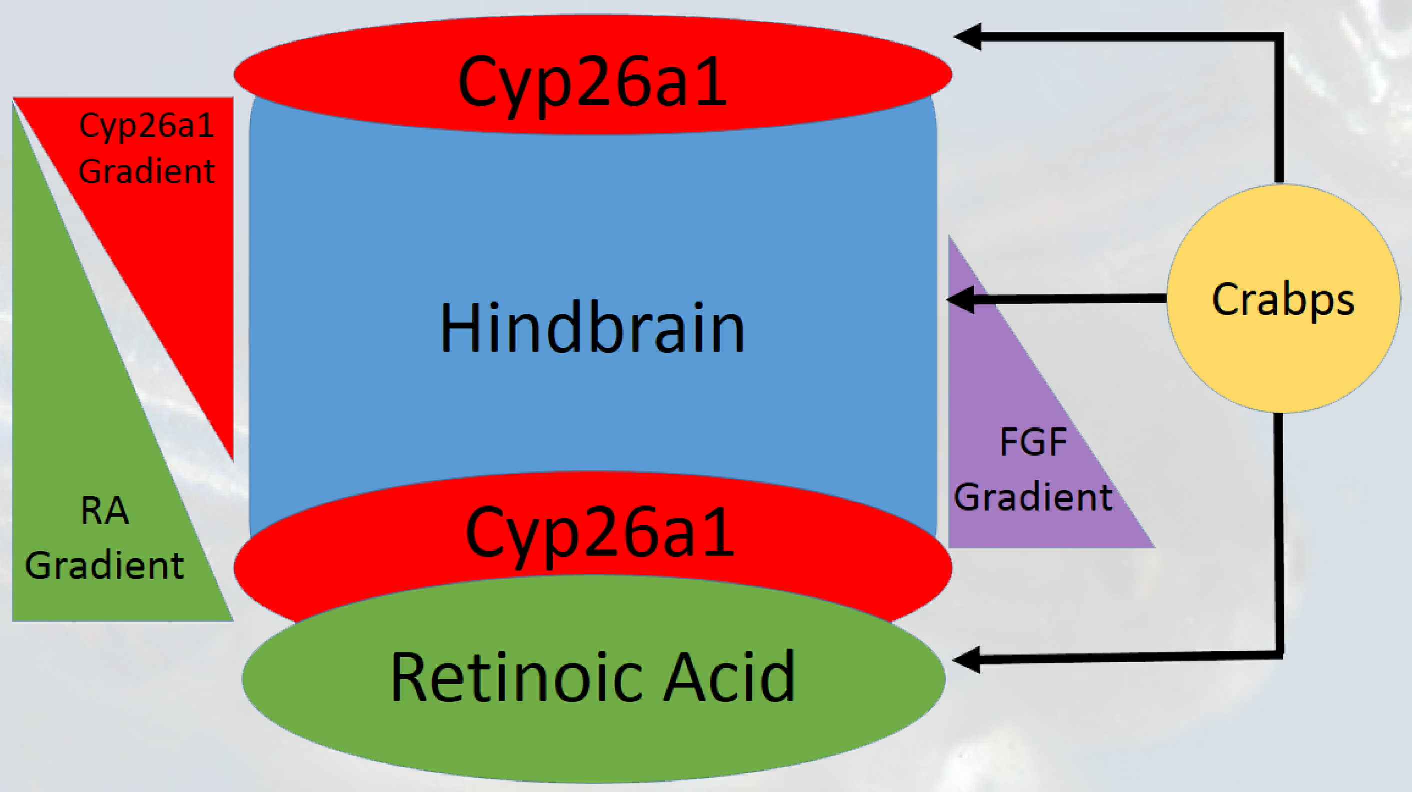
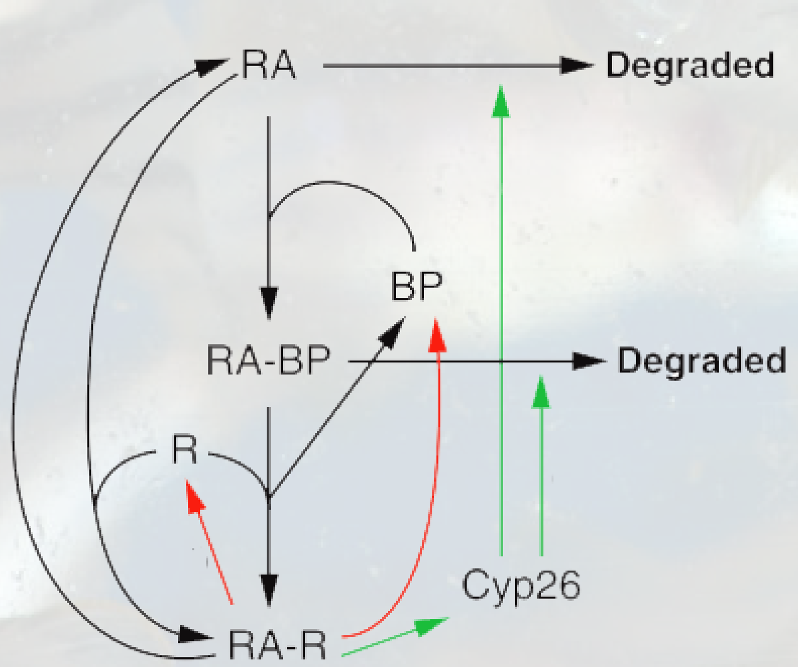
The Zebrafish Hindbrain

- The hindbrain is segmented due to spatial patterning of the Hox genes.
- This portion of the brain, known as the "hindbrain" or the "brainstem", collectively regulates vital bodily processes such as breathing, swallowing, blood circulation, and muscle tone.
- Signals produced by mesoderm lying posterior to the hindbrain include RA, and FGF, which with the help of the HOX genes help divide the hindbrain into rhombomeres.
- We wish to understand how noise contributes and is regulated within this spatial patterning network.



The Interaction Network

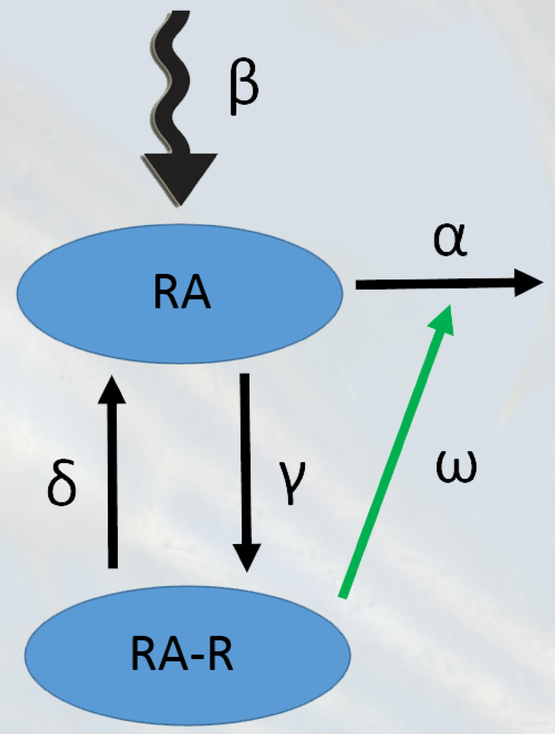
- Cells unleash RA from nutrients in the yolk.
- Cyp26a1 is an intracellular (non-diffusive) molecule which degrades RA.
- Receptor-bound RA (RA-R) upregulates the production of Cyp26a1, creating a self-enhanced degradation loop.
- Cellular retonoic acid binding proteins (Crabps) can both help deliver RA to its receptors as well as deliver it to Cyp26s for degradation. One of these, Crabp2a, is also induced by RA and can increase self-enhanced degradation.



Phenomenological Model

We wish to model the effects of the cellular retinoic acid binding proteins (crabps) and Cyp26a1 on the noise of the RA gradient in zebrafish hindbrain development.

- Assume the regulation of RA is Michaelis-Menton.
- Let η, the basal rate of RA degradation, be a "small but not insignificant" constant.
- Let $[Crabp]$ effect the binding of RA to RA-R and of Cyp26a1 to RA linearly.
- Let $[Cyp]_{max}$ be the maximum upreglated Cyp26 due to RA-R.



$$
\begin{aligned}
d[RA] &= [\beta - \left(\frac{\alpha_0 [Cyp]_{max}[RA-R]}{\omega_0/[Crabp]+\omega_1+[RA-R]} + \gamma_0[Crabp] + \gamma_b + \eta\right)[RA] \\
&\quad +\delta[RA-R]]dt + \sigma dW_t \\
d[RA-R] &= ((|\gamma_0[Crabp]+\gamma_b)[RA] - \delta[RA-R])\,dt \\
d[Crabp] &= 0
\end{aligned}
$$

The Fluctuation-Dissipation Theorem

We can write a system of stochastic differential equations as

$$dX = \mu(X,t)dt + \Gamma(X,t)dW_t,$$

Take the Jacobian of the deterministic system around a steady state X_{ss} to get

$$dX = J_\mu(X_{ss},t)dt + \Gamma(X_{ss},t)dW_t.$$

The Fluctuation-Dissipation Theorem states that the variance-covariance matrix, Σ, can be found using the formula

$$J_\mu(X_{ss},t)\Sigma(X_{ss},t) + \Sigma(X_{ss},t)J_\mu^T(X_{ss},t) = -\Gamma^2(X_{ss},t).$$

Solution

WLOG, $\delta = 1$. Define the function:

$$\sigma^2_{[RA]}(\alpha,\beta,\omega,\eta,\delta,\gamma) \approx \sigma^2 f(\alpha,\beta,\eta,\omega,\gamma)$$

Since during Crabp2a knockdown $\alpha \gg 1$, $\frac{\partial f}{\partial \omega} \approx 0$.
Let the total change from a knockdown be defined as

$$\Delta_\zeta f = |\lim_{\zeta\to\infty} f - \lim_{\zeta\to 0} f|.$$

$$\Delta_\alpha f = \frac{2(1+\eta)}{4\eta(\gamma+1+\eta)} = \frac{1}{2\eta}\frac{1+\eta}{\gamma+1+\eta} \approx 0$$

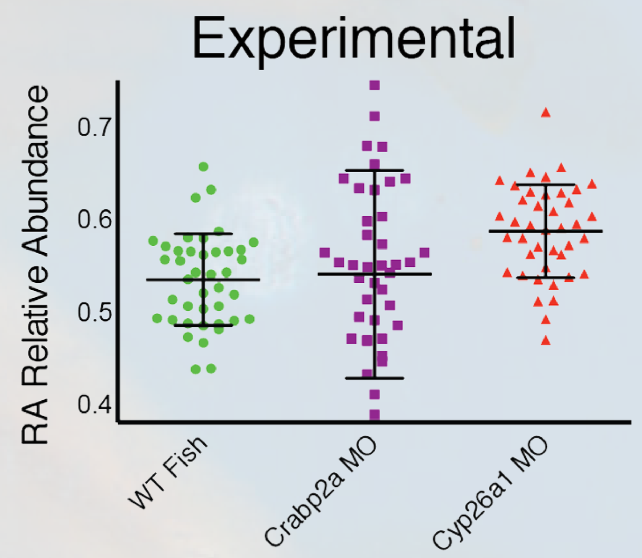
if $\gamma \gg \frac{1}{\eta}$ during Cyp knockdown. And since $\alpha \gg 1$ during Crab knockdown,

$$\Delta_\gamma f \approx \frac{1}{2\eta}$$

which is large if $\eta \ll 1$.

Conclusions

- We assume the basal rate of RA degradation is "small but not insignificant" and the binding rate of RA to RA-R is large.
- Knockdown of Cyp26a1:
  - The mean increases.
  - The variance is unchanged.
- Knockdown of Crabp2a:
  - The mean is unchanged.
  - The variance increases.



Future Directions

- Incorporate additional effects into the model.
  - RA upregulates Crabp2a.
  - There limited amounts of receptors.
- Investigate the effects of Cyp26b1 and Crabp2b proteins.
- Examine the regulatory effects due to transcriptional delays mathematically.
- Determine the color of the noise.
  - Mathematically determine the approximate color of the noise.
  - Investigate whether the color of the noise holds any information such as temporal delays.
  - Develop an experimental method in order to accurately measure noise frequencies.
- Examine the spatial properties of the noise.
  - Extend the model to a spatial dimension.
  - Perturb the spatial noise using mosaic spatial misexpression experiments.
- Look into the transition events in hindbrain development.
  - Examine both mathematically and experimentally critical transition behaviors through the autocorrelation lags, variance changes, "flickering", spatial coherence.

Acknowledgments

This investigation was supported by the National Institute of Biomedical Imaging and Bioengineering, National Research Service Award EB009418 from the University of California, Irvine, Center for Complex Biological Systems. I would like to thank Professor Qing Nie for his mentorship and Dr. Julian Sosnik for his time and effort.