Stochastic Yan Network Modeling

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Apr 6, 2015

1 General Strategy

As outlined in our recent proposal, we aim to perform detailed stochastic simulations to investigate noise profiles experimentally observed for Yan in the developing fly eye.

2 Model Components

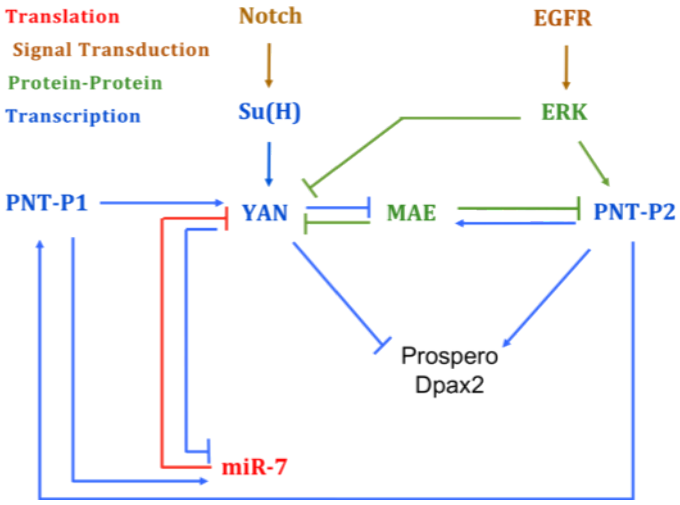
2.1 Input

1. **Notch signaling** [N] via Su(H) that controls Yan transcription.
2. **EGFR signaling** via ERK/Mapk [E] that controls PntP2 and Yan phosphorylation.

2.2 Interacting Species

1. **Yan** $[Y]$ explicitly model Yan transcription, translation, phosphorylation, and dimerization.
2. **PntP1** $[P_1]$
3. **PntP2** $[P_2]$ model phosphorylation via dpMapk
4. **Mae** $[M]$
5. **mir-7** $[m_{R7}]$

2.3 Interaction Schematic



3 Model Reactions

Following notation from Graham et al. 2010. To simplify the numbers of reactions and rates we are accounting for, we can consider a stochastic model with certain intermediaries implicitly accounted for by quasi-steady state assumptions. Two candidate groups of reactions for this approximation include ERK phosphorylation and Yan/Pnt DNA binding.

3.1 Yan Reactions

3.1.1 Yan Induction

$$\begin{aligned} m_Y &\xrightarrow{h_{m_Y}} m_Y + 1 \\ h_{m_Y} &= N(t) + E_{m_Y}(Y, Y : Y, P_1, P_{2P}) \end{aligned} \tag{1}$$

Time-dependent activation by Notch as well as equilibrium transcription factor activity based on DNA binding. The general pattern for representing the expected transcriptional activity for species A with promoter states $s \in S$ with multiplicity $M(s)$:

$$\begin{aligned} E_A(\dots) &= \sum_{s \in S} \alpha_s P(s) \\ P(s) &= \frac{M(s) e^{-\Delta G_s / kT}}{Z} \\ Z &= \sum_{s \in S} M(s) e^{-\Delta G_s / kT} \end{aligned}$$

For Yan, Mae, and mir-7, we have 5 promoter states: unbound, single Yan bound, Yan dimer bound, PntP1 bound, PntP2-P bound. These all require an activity level and boltzmann weight to be specified.

$$\begin{aligned} Y &\xrightarrow{h_Y} Y + 1 \\ h_Y &= k_Y m_Y \end{aligned} \tag{2}$$

Production of Yan protein from transcript.

3.1.2 Yan Dimerization

$$Y + Y \underset{\overleftarrow{k_{Y:Y}}}{\overrightleftharpoons{\overrightarrow{k_{Y:Y}}}} Y:Y \tag{3}$$

3.1.3 Yan Phosphorylation

$$\begin{aligned} M:Y &\xrightarrow{h_{Y_P}} M:Y_P \\ h_{Y_P} &= G_Y(E(t)) \end{aligned} \tag{4}$$

Yan phosphorylation requires Mae binding (as in Graham et al. 2010). Level of dpMapk, $E(t)$, is time dependent. Default Michaelis-Menten phosphorylation rate:

$$G_A(B) = \frac{\alpha_A B A}{K_A + A}$$

3.1.4 Yan Interactions

$$m_Y + m_{R7} \underset{\overleftarrow{k_{m_Y:m_{R7}}}}{\overrightleftharpoons{\overrightarrow{k_{m_Y:m_{R7}}}}} m_Y:m_{R7} \tag{5}$$

Sequestration of Yan transcript by mir-7.

$$Y + M \underset{\overleftarrow{k_{M:Y}}}{\overrightleftharpoons{\overrightarrow{k_{M:Y}}}} M:Y \tag{6}$$

$$Y_P + M \underset{\overleftarrow{k_{M:Y_P}}}{\overrightleftharpoons{\overrightarrow{k_{M:Y_P}}}} M:Y_P \tag{7}$$

Yan complex with Mae. Dissociation of phosphorylated complex ought to be rapid ($\overleftarrow{k_{M:Y_P}} \gg \overleftarrow{k_{M:Y}}$).

3.2 Pnt Reactions

$$P_2 \xrightarrow{h_{P_2}} P_2 + 1 \tag{8}$$
$$h_{P_2} = e_{P_2}$$

PntP2 simply produced at a constant rate.

$$P_2 \xrightarrow{h_{P_{2P}}} P_{2P} \tag{9}$$
$$h_{P_{2P}} = G_{P_2}(E(t))$$

PntP2 activation by phosphorylation depends on time-dependent dpMapk signal (as did Yan phosphorylation).

$$P_{2P} + M \underset{\overleftarrow{k_{M:P_{2P}}}}{\overset{\overrightarrow{k_{M:P_{2P}}}}{\rightleftharpoons}} M : P_{2P} \tag{10}$$

PntP2-P is bound by Mae and sequestered.

$$P_1 \xrightarrow{h_{P_1}} P_1 + 1 \tag{11}$$
$$h_{P_1} = \frac{\alpha_{P_1} P_{2P}^{n_{P_1}}}{k_{P_1}^{n_{P_1}} + P_{2P}^{n_{P_1}}} + e_{P_1}$$

PntP1 production is induced by PntP2-P, using Hill function approximation.

3.3 Mae/mir-7 Reactions

$$M \xrightarrow{h_M} M + 1 \tag{12}$$
$$h_M = E_M(Y, Y : Y, P_1, P_{2P})$$

$$m_{R7} \xrightarrow{h_{m_{R7}}} m_{R7} + 1 \tag{13}$$
$$h_{m_{R7}} = E_{m_{R7}}(Y, Y : Y, P_1, P_{2P})$$

Both Mae and mir-7 production are governed by transcription factor DNA binding similarly to Yan.

3.4 Complex Assembly and Disassembly

All complex assembly and disassembly reactions follow standard mass action kinetics.

3.5 Degradation

For each component there is also a degradation reaction with a rate that follows first-order kinetics.

4 Reaction Parameters

Some parameter estimates presented in Matt Hope presentation (Nov 11, 2014):

Concentration Range	0.1nM - 100nM	5-5000 copies
Yan-DNA ETS binding	56nM	-9.955 kcal/mol
Yan-DNA non-specific binding	50uM	-5.837 kcal/mol
SAM domain interaction	7uM	-7.043 kcal/mol

Some other parameter estimates presented in Lauren Cote presentation (December 2, 2010):

Yan-DNA ETS binding	1nM	-12.27 kcal/mol
SAM domain interaction	10uM	-6.816 kcal/mol
Yan-Mae interaction	10nM	-10.91 kcal/mol
Pnt-DNA binding	1uM	-8.179 kcal/mol
Yan-bound site	low mRNA production	
unbound site	medium mRNA production	
Pnt-bound site	high mRNA production	
S2 cell nucleus	78 um^3	

4.1 Parameter Assumptions

1. Default protein mean lifetime 1hr – perhaps this could be estimated from the experimental data given that the degradation rate determines time to equilibrium copy number. For phosphorylated Yan this is assumed to be 5 min

2. Default mRNA mean lifetime 10min

3. Mean phosphorylation time per dpMapk 1min

4. Complex mean lifetime 5min. Mae-YanP is assumed to rapidly dissociate with mean lifetime 30sec

5. Protein copy number 500

6. RNA copy number 20

5 Alternative Formulations

An alternative formulation for Yan induction could follow approximate Michaelis Menten kinetics for competitive inhibition:

$$h_{m_Y} = N(t) + F_{m_Y}(Y : Y, P_1)$$

Yan self-repression via competitive inhibition, activation by PntP1, interaction with mir-7. Hill function defaults (for species A,B,C):

$$F_A(B, C) = \frac{\alpha_A C^{n_A}}{k_A^{n_A}(1 + (B/k_B)^{m_A}) + C^{n_A}} + e_A$$

A more explicit formulation would treat different binding states in the Yan, Mae, and mir-7 promotors as different species and stochastically model their occupancy.