Full set of reactions for the transcription model

1. **Open-closed** state transitions for promoter, enhancer, and silencer:

$$\mathrm{P_{closed}} \underset{k_{\mathrm{P\_off}}}{\overset{k_{\mathrm{P\_on}}}{\rightleftharpoons}} \mathrm{P_{open}}$$

$$\mathrm{E_{closed}} \underset{k_{\mathrm{E\_off}}}{\overset{k_{\mathrm{E\_on}}}{\rightleftharpoons}} \mathrm{E_{open}}$$

$$\mathrm{S_{closed}} \underset{k_{\mathrm{S\_off}}}{\overset{k_{\mathrm{S\_on}}}{\rightleftharpoons}} \mathrm{S_{open}}$$

2. **Transcription factor binding** reactions for promoter:

$$\mathrm{P_{open}} + \mathrm{TF_P} \underset{k_{\mathrm{TF\_Punbind}}}{\overset{k_{\mathrm{TF\_Pbind}}}{\rightleftharpoons}} [\mathrm{P_{open}} \cdot \mathrm{TF_P}]$$

$$\mathrm{E_{open}} + \mathrm{TF_E} \underset{k_{\mathrm{TF\_Eunbind}}}{\overset{k_{\mathrm{TF\_Ebind}}}{\rightleftharpoons}} [\mathrm{E_{open}} \cdot \mathrm{TF_E}]$$

$$\mathrm{S_{open}} + \mathrm{TF_S} \underset{k_{\mathrm{TF\_Sunbind}}}{\overset{k_{\mathrm{TF\_Sbind}}}{\rightleftharpoons}} [\mathrm{S_{open}} \cdot \mathrm{TF_S}]$$

3. **Interaction of TF-bound complexes** with promoter complex. For enhancer+TF complex:

$$[\mathrm{E_{open}} \cdot \mathrm{TF_E}] + [\mathrm{P_{open}} \cdot \mathrm{TF_P}] \underset{k_{\mathrm{EPunbind}}}{\overset{k_{\mathrm{EPbind}}}{\rightleftharpoons}} [\mathrm{E_{open}} \cdot \mathrm{TF_E} \cdot \mathrm{P_{open}} \cdot \mathrm{TF_P}]$$

$$[\mathrm{S_{open}} \cdot \mathrm{TF_S}] + [\mathrm{P_{open}} \cdot \mathrm{TF_P}] \underset{k_{\mathrm{SPunbind}}}{\overset{k_{\mathrm{SPbind}}}{\rightleftharpoons}} [\mathrm{S_{open}} \cdot \mathrm{TF_S} \cdot \mathrm{P_{open}} \cdot \mathrm{TF_P}]$$

4. **Transcription** reactions

Default transcription from open promoter: $[\mathrm{P_{open}} \cdot \mathrm{TF_P}] \xrightarrow{ktr_{\mathrm{const}}} \left[P_{\mathrm{open}}\, TF_{\mathrm{P}}\right] + x$
Activated transcription from binding of enhancer complex:

$$[\mathrm{E_{open}} \cdot \mathrm{TF_E} \cdot \mathrm{P_{open}} \cdot \mathrm{TF_P}] \xrightarrow{ktr_{\mathrm{act}}} \left[E_{\mathrm{open}}\, TF_{\mathrm{E}}\, P_{\mathrm{open}}\, TF_{\mathrm{P}}\right] + x$$

Decay reaction: $\mathrm{x} \xrightarrow{\delta} \emptyset$

We assume that silencer complex works as competitive inhibitor and can bind some open promoters thus restricting their interaction with the enhancer complex. Therefore we don't have transcription reaction from the promoter-silencer complex.

Full set of equations for the transcription model

Initial model

$$\begin{cases} dA_i/dt = k_{on,i} I_i - k_{off,i} A_i \\ dI_i/dt = k_{off,i} A_i - k_{on,i} I_i \\ dx_i/dt = \phi_i s_i A_i - \delta_i x_i \end{cases} \tag{1}$$

where for gene i: A_i - active state of promoter, I_i - inactive state of promoter, $k_{on,i}$ - , $k_{off,i}$, ϕ_i - , s_i - , δ_i - decay rate.

Our model

1. **Open-closed** state transitions for promoter, enhancer, and silencer:

$$\begin{cases} dP_{open,i}/dt = k_{Pon,i} P_{closed,i} - k_{Poff,i} P_{open,i} \\ dP_{closed,i}/dt = k_{Poff,i} P_{open,i} - k_{Pon,i} P_{closed,i} \end{cases} \tag{2}$$

$$\begin{cases} dE_{open,i}/dt = k_{Eon,i} E_{closed,i} - k_{Eoff,i} E_{open,i} \\ dE_{closed,i}/dt = k_{Eoff,i} E_{open,i} - k_{Eon,i} E_{closed,i} \end{cases} \tag{3}$$

$$\begin{cases} dS_{open,i}/dt = k_{Son,i} S_{closed,i} - k_{Soff,i} S_{open,i} \\ dS_{closed,i}/dt = k_{Soff,i} S_{open,i} - k_{Son,i} S_{closed,i} \end{cases} \tag{4}$$

2. **Transcription factor binding** reactions for promoter:

$$\begin{cases} d[P_{open,i}TF_P]/dt = k_{TF_Pbind,i}P_{open,i} - k_{TF_Punbind,i}P_{open,i} \\ dP_{open,i}/dt = k_{TF_Punbind,i}[P_{open,i}TF_P] - k_{TF_Pbind,i}P_{open,i}TF_P \\ dTF_P/dt = k_{TF_Punbind,i}[P_{open,i}TF_P] - k_{TF_Pbind,i}P_{open,i}TF_P \end{cases} \tag{5}$$

For enhancer:

$$\begin{cases} d[E_{open,i}TF_E]/dt = k_{TF_Ebind,i}E_{open,i} - k_{TF_Eunbind,i}E_{open,i} \\ dE_{open,i}/dt = k_{TF_Eunbind,i}[E_{open,i}TF_E] - k_{TF_Ebind,i}E_{open,i}TF_E \\ dTF_E/dt = k_{TF_Eunbind,i}[E_{open,i}TF_E] - k_{TF_Ebind,i}E_{open,i}TF_E \end{cases} \tag{6}$$

For silencer:

$$\begin{cases} d[S_{open,i}TF_S]/dt = k_{TF_Sbind,i}S_{open,i} - k_{TF_Sunbind,i}S_{open,i} \\ dS_{open,i}/dt = k_{TF_Sunbind,i}[S_{open,i}TF_S] - k_{TF_Sbind,i}S_{open,i}TF_S \\ dTF_S/dt = k_{TF_Sunbind,i}[S_{open,i}TF_S] - k_{TF_Sbind,i}S_{open,i}TF_S \end{cases} \tag{7}$$

3. **Interaction of TF-bound complexes** with promoter complex. For enhancer+TF complex:

$$\begin{cases} d[E_{open,i}TF_E * P_{open,i}TF_P]/dt = k_{EPbind,i}[E_{open,i}TF_E][P_{open,i}TF_P] - k_{EPunbind,i}[E_{open,i}TF_E * P_{open,i}TF_P] \\ d[E_{open,i}TF_E]/dt = k_{EPunbind,i}[E_{open,i}TF_E * P_{open,i}TF_P] - k_{EPbind,i}[E_{open,i}TF_E][P_{open,i}TF_P] \\ d[P_{open,i}TF_P]/dt = k_{EPunbind,i}[E_{open,i}TF_E * P_{open,i}TF_P] - k_{EPbind,i}[E_{open,i}TF_E][P_{open,i}TF_P] \end{cases} \tag{8}$$

For silencer+TF complex:

$$\begin{cases} d[S_{open,i}TF_S * P_{open,i}TF_P]/dt = k_{SPbind,i}[S_{open,i}TF_S][P_{open,i}TF_P] - k_{SPunbind,i}[S_{open,i}TF_S * P_{open,i}TF_P] \\ d[S_{open,i}TF_S]/dt = k_{SPunbind,i}[S_{open,i}TF_S * P_{open,i}TF_P] - k_{SPbind,i}[S_{open,i}TF_S][P_{open,i}TF_P] \\ d[P_{open,i}TF_P]/dt = k_{SPunbind,i}[S_{open,i}TF_S * P_{open,i}TF_P] - k_{EPbind,i}[S_{open,i}TF_S][P_{open,i}TF_P] \end{cases} \tag{9}$$

4. **Transcription** equations
Option 1, transcription and decay:

$$dx_i/dt = \phi_i([E_{open,i}TF_E * P_{open,i}TF_P] - [S_{open,i}TF_S * P_{open,i}TF_P]) - \delta_i x_i \tag{10}$$

Option 2, transcription and decay:

$$dx_i/dt = \phi_i(P_{open,i} + amp\frac{1 + [E_{open,i}TF_E * P_{open,i}TF_P]}{1 + [S_{open,i}TF_S * P_{open,i}TF_P]}) - \delta_i x_i \tag{11}$$

We can simplify these set of equations by writing down cumulative expression for each component. For promoter reactants:

$$\begin{cases} dP_{open,i}/dt = k_{Pon,i}P_{closed,i} - k_{Poff,i}P_{open,i} + k_{TF_Punbind,i}[P_{open,i}TF_P] - k_{TF_Pbind,i}P_{open,i}TF_P \\ dP_{closed,i}/dt = k_{Poff,i}P_{open,i} - k_{Pon,i}P_{closed,i} \\ d[P_{open,i}TF_P]/dt = k_{TF_Pbind,i}P_{open,i} - k_{TF_Punbind,i}P_{open,i} + k_{EPunbind,i}[E_{open,i}TF_E * P_{open,i}TF_P] - \\ -k_{EPbind,i}[E_{open,i}TF_E][P_{open,i}TF_P] + k_{SPunbind,i}[S_{open,i}TF_S * P_{open,i}TF_P] - k_{EPbind,i}[S_{open,i}TF_S][P_{open,i}TF_P] \\ dTF_P/dt = k_{TF_Punbind,i}[P_{open,i}TF_P] - k_{TF_Pbind,i}P_{open,i}TF_P \end{cases} \tag{12}$$

For only enhancer reactants:

$$\begin{cases} dE_{open,i}/dt = k_{Eon,i}E_{closed,i} - k_{Eoff,i}E_{open,i} + k_{TF_Eunbind,i}[E_{open,i}TF_E] - k_{TF_Ebind,i}E_{open,i}TF_E \\ dE_{closed,i}/dt = k_{Eoff,i}E_{open,i} - k_{Eon,i}E_{closed,i} \\ d[E_{open,i}TF_E]/dt = k_{TF_Ebind,i}E_{open,i} - k_{TF_Eunbind,i}E_{open,i} + k_{EPunbind,i}[E_{open,i}TF_E * P_{open,i}TF_P] - \\ -k_{EPbind,i}[E_{open,i}TF_E][P_{open,i}TF_P] \\ dTF_E/dt = k_{TF_Eunbind,i}[E_{open,i}TF_E] - k_{TF_Ebind,i}E_{open,i}TF_E \\ d[E_{open,i}TF_E * P_{open,i}TF_P]/dt = k_{EPbind,i}[E_{open,i}TF_E][P_{open,i}TF_P] - k_{EPunbind,i}[E_{open,i}TF_E * P_{open,i}TF_P] \end{cases} \tag{13}$$

For only silencer reactants:

$$\begin{cases} dS_{open,i}/dt = k_{Son,i}S_{closed,i} - k_{Soff,i}S_{open,i} \\ dS_{closed,i}/dt = k_{Soff,i}S_{open,i} - k_{Son,i}S_{closed,i} + k_{TF_Sunbind,i}[S_{open,i}TF_S] - k_{TF_Sbind,i}S_{open,i}TF_S \\ d[S_{open,i}TF_S]/dt = k_{TF_Sbind,i}S_{open,i} - k_{TF_Sunbind,i}S_{open,i} + k_{SPunbind,i}[S_{open,i}TF_S * P_{open,i}TF_P] - \\ -k_{SPbind,i}[S_{open,i}TF_S][P_{open,i}TF_P] \\ dTF_S/dt = k_{TF_Sunbind,i}[S_{open,i}TF_S] - k_{TF_Sbind,i}S_{open,i}TF_S \\ d[S_{open,i}TF_S * P_{open,i}TF_P]/dt = k_{SPbind,i}[S_{open,i}TF_S][P_{open,i}TF_P] - k_{SPunbind,i}[S_{open,i}TF_S * P_{open,i}TF_P] \end{cases} \tag{14}$$

It is important to notice that here we are using separated pulls of transcription factors for promoters, silencers, and enhancers. However, in the real life each region might have binding motif for several different TFs, thus making some of Tfs behave as both positive and negative regulators. We have created advanced versions of our model inspired by previously described GRN models from [mention 3 articles] to account for it.

We can simplify these set of equations by writing down cumulative expression for each component. For promoter reactants:

$$\begin{cases} dP_{open,i}/dt = k_{Pon,i}P_{closed,i} - k_{Poff,i}P_{open,i} + k_{TF_Punbind,i}[P_{open,i}TF_P] - k_{TF_Pbind,i}P_{open,i}TF_P \\ dP_{closed,i}/dt = k_{Poff,i}P_{open,i} - k_{Pon,i}P_{closed,i} \\ d[P_{open,i}TF_P]/dt = k_{TF_Pbind,i}P_{open,i} - k_{TF_Punbind,i}P_{open,i} + k_{EPunbind,i}[E_{open,i}TF_E * P_{open,i}TF_P] - \\ -k_{EPbind,i}[E_{open,i}TF_E][P_{open,i}TF_P] + k_{SPunbind,i}[S_{open,i}TF_S * P_{open,i}TF_P] - k_{SPbind,i}[S_{open,i}TF_S][P_{open,i}TF_P] \\ dTF_P/dt = k_{TF_Punbind,i}[P_{open,i}TF_P] - k_{TF_Pbind,i}P_{open,i}TF_P \end{cases} \tag{15}$$

If we assume that there are no silencers and enhancers in our model, we can simply set all related rate constants and initial concentrations to zeros. Therefore there will be only promoter-related equations left and a transcription equation itself:

Promotor:

$$\begin{cases} dP_{open,i}/dt = k_{Pon,i}P_{closed,i} - k_{Poff,i}P_{open,i} + k_{TF_Punbind,i}[P_{open,i}TF_P] - k_{TF_Pbind,i}P_{open,i}TF_P \\ dP_{closed,i}/dt = k_{Poff,i}P_{open,i} - k_{Pon,i}P_{closed,i} \\ d[P_{open,i}TF_P]/dt = k_{TF_Pbind,i}P_{open,i} - k_{TF_Punbind,i}P_{open,i} \\ dTF_P/dt = k_{TF_Punbind,i}[P_{open,i}TF_P] - k_{TF_Pbind,i}P_{open,i}TF_P \end{cases} \tag{16}$$

Transcription (option 2), transcription and decay:

$$dx_i/dt = ktr_{const} * P_{open,i}TF_P + ktr_{act}\frac{1 + [E_{open,i}TF_E * P_{open,i}TF_P]}{1 + [S_{open,i}TF_S * P_{open,i}TF_P]}) - \delta_i x_i \tag{17}$$