Models with simplified dynamics

General ODE model for genetic network
\[
\dot{x}_i = f_i(x) - \gamma_i x_i
\]
- Functions \( f_i(x) \) are sigmoidal

Piecewise-Linear Differential Equations
- Replaces sigmoidal functions with piecewise constant functions
\[
f_i(x) = \sum_{l=1}^{L} \kappa_{il} b_{il}(x)
\]
Where \( \kappa_{il} > 0 \), is a rate parameter, \( b_{il} : \mathbb{R}^n \to \{0,1\} \) are functions specified by means of Heaviside step functions \( s^\pm(x_j, \theta_j) \) with thresholds \( \theta_j \)
\[
s^+(x_j, \theta_j) = \begin{cases} 
0 & x_j < \theta_j \\
1 & x_j \geq \theta_j
\end{cases}
\]
\[
s^-(x_j, \theta_j) = 1 - s^+(x_j, \theta_j)
\]

Ex:
\[
\begin{align*}
\dot{x}_1 &= \kappa_1 s^+(x_2, \theta_{21}) - \gamma_1 x_1 \\
\dot{x}_2 &= \kappa_2 (1 - s^+(x_1, \theta_{11})s^+(x_3, \theta_{31})) - \gamma_2 x_2 \\
\dot{x}_3 &= \kappa_3 s^-(x_1, \theta_{12}) - \gamma_3 x_3
\end{align*}
\]

Behavior of PLDE
Consider the \( n \)-dimensional hyperbox \( B = \left\{ x \mid 0 \leq x_i \leq \max_{x \geq 0} \max_{j} f_j(x), \theta_{jk} \right\} \)
Hyperplanes \( x_j = \theta_{jk} \) divide \( B \) into subdomains on which the system is piecewise linear with constant production terms:
\[
\dot{x}_i = \mu_i - \gamma_i x_i
\]
Focal state of a subdomain: \( x_i^* = \mu_i / \gamma_i \)
- If a focal state is in the corresponding subdomain, it is a regular fixed point that is stable.
• *Singular* fixed points may exist on threshold planes.
• Global behavior may include cycles, limit cycles, or chaos (for \( n \geq 4 \))

**Qualitative behavior**
• Represents dynamics as a graph of transitions between states

**Ex:** Mutually repressing and self-repressing genes

\[
\dot{x}_a = \kappa_a s^-(x_a, \theta_a^1) s^-(x_b, \theta_b^1) - \gamma_a x_a \\
\dot{x}_b = \kappa_b s^-(x_a, \theta_a^1) s^-(x_b, \theta_b^2) - \gamma_b x_b
\]

\[
\theta_a^1 < \theta_a^2 \\
\theta_b^1 < \theta_b^2
\]
Generalized Logical Networks

- Replace real valued variables with discrete valued (e.g., \( x_i \in \{0,1\} \))
- Replace sigmoidal functions with Boolean functions (see Lecture 18)
- Replace dynamics with discrete “tendency” dynamics

\[ X_i = f_i(x'_1, \ldots, x'_n) \]

is interpreted as \( x'_i \) will have a tendency to change to \( x'_{i+1} = X_i \)

- Only one of the variables can change during a time step (asynchronous update)

\[ Ex: \text{ Positive feedback} \]

\[
\begin{array}{c|c|c}
 x_1, x_2, x_3 & X_1, X_2, X_3 \\
--- & --- \\
 000 & 011 \\
 001 & 111 \\
 010 & 010 \\
 011 & 110 \\
 100 & 001 \\
 101 & 101 \\
 110 & 000 \\
 111 & 100 \\
\end{array}
\]

\[ Ex: \text{ Negative feedback} \]

\[
\begin{array}{c|c|c}
 x_1, x_2, x_3 & X_1, X_2, X_3 \\
--- & --- \\
 000 & 100 \\
 001 & 000 \\
 010 & 101 \\
 011 & 001 \\
 100 & 110 \\
 101 & 010 \\
 110 & 111 \\
 111 & 011 \\
\end{array}
\]
Global dynamics:

- Stable fixed points $x_i^i = f_i(x)^i$, stable and unstable cycles
- Unstable fixed points are absent as they lie at the threshold levels – requires extending the logical variables to include the thresholds.

Example applications: (for references see de Jong, 2002)

**ODEs**
- $\lambda$-phage switch *cro-cII*
- *lac* operon
- developmental cycle of bacteriophage T7
- trp synthesis
- circadian rhythms in *Drosophila*
- cell cycle – mitosis in *Xenopus* oocyte

**PLDEs**
- tryptophan synthesis and arabinosis regulation in *E.coli*
- sporulation in *Bacilus subtilis*

**Generalized logical networks**
- $\lambda$-phage switch
- pattern formation and gap control in *Drosophila* development
- flower morphogenesis in *Arabidopsis*

**Boolean networks**
- segmentation in *Drosophila*
- Large scale network behavior