Kara DeSouza
Kyle McDermott
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Kauffman 1969 – Metabolic Stability and Epigenesis in Randomly Constructed Genetic Nets

1. Introduction
   - Main proposal: that randomly connected feedback nets of binary genes behave in ways comparable to living systems
   - Once built, initially randomly assigned inputs to each gene remain fixed, as does their initially random effect on its output (number of possible Boolean functions = $2^{2^\wedge K}$ where K is the number of inputs)
   - A switching net free of external inputs, or with constant external inputs (e.g. bacterium or sea urchin in homogeneous surroundings) undergo autonomous changes
2. Genetic Model
   - A gene's output, based on one, and only one, of the possible $2^{2^\wedge K}$ functions will be 0 or 1 for all of its outputs at time $T + 1$ based on its input at time T
   - A cycle length is the number of states on a re-enterant cycle
   - A transient length is the number of states before the first state encountered on a cycle
   - A confluent is the set of states leading into, or on, a cycle
   - A formal genetic net must have at least one cycle, and multiple cycles can only be reached with different initial inputs
3. Totally Connected Nets, $K = N$
   - The cycle length of a totally connected net with 200 elements and 2^{200} states is ~10^{30} states, making totally connected random nets biologically impossible
4. One Connected Nets, $K = 1$
   - State cycles exceed several million states, also not realistic
5. Two Connected Nets, $K = 2$
   - Cycles tend to be short, though removing tautology (always 1) and contradiction (always 0) functions spreads the distribution away from peaking at <5 states per cycle
   - Run-in lengths are not correlated with cycle lengths
   - Using all Boolean functions, 0 to 35 genes vary during a cycle in a net of 100 elements
   - The number of possible cycles per net tends to be very low
   - If a cycle is considered a state of a Markov chain, then an ergodic set of cycles is one in which each cycle can reach all the others in a set but no others outside the set (transient cycles lie outside any of these sets)
   - An absorbing cycle is a set that contains only itself, it will always return to itself when perturbed
   - Most cycles return to themselves when perturbed 85-95% of the time
7. Cell Cycle Time
   - Plant studies show a linear relation between length of DNA content and the minimum cell replication time
   - Plotting cycles from the genetic net along with cell replication times of living organisms as a function of length show similarities, suggesting real genetic nets can arise from random initialization
8. Cellular Differentiation
   - Cell type is identified by a particular cycle
   - The predictions made from random genetic nets "remain well within an order of magnitude" of living systems
   - The number of different cycles a perturbed cycle can move to is similar to the number of different cell types any one cell type can differentiate to

Clarifications

- Confluent – can be viewed as analogous to the basins of attraction one might imagine within parameter space. Once in a state within this basin the system will fall into the related cycle
- Figure 2c – There is a missing step between the state (100) and (001), it should be (100) -> (000) -> (001). Adding that results in all 8 possible states being represented in a complete diagram
- Minimum distance between cycles can be viewed as shortest distance in parameter space between the two cycles (as per Prof. Doursat's diagram)