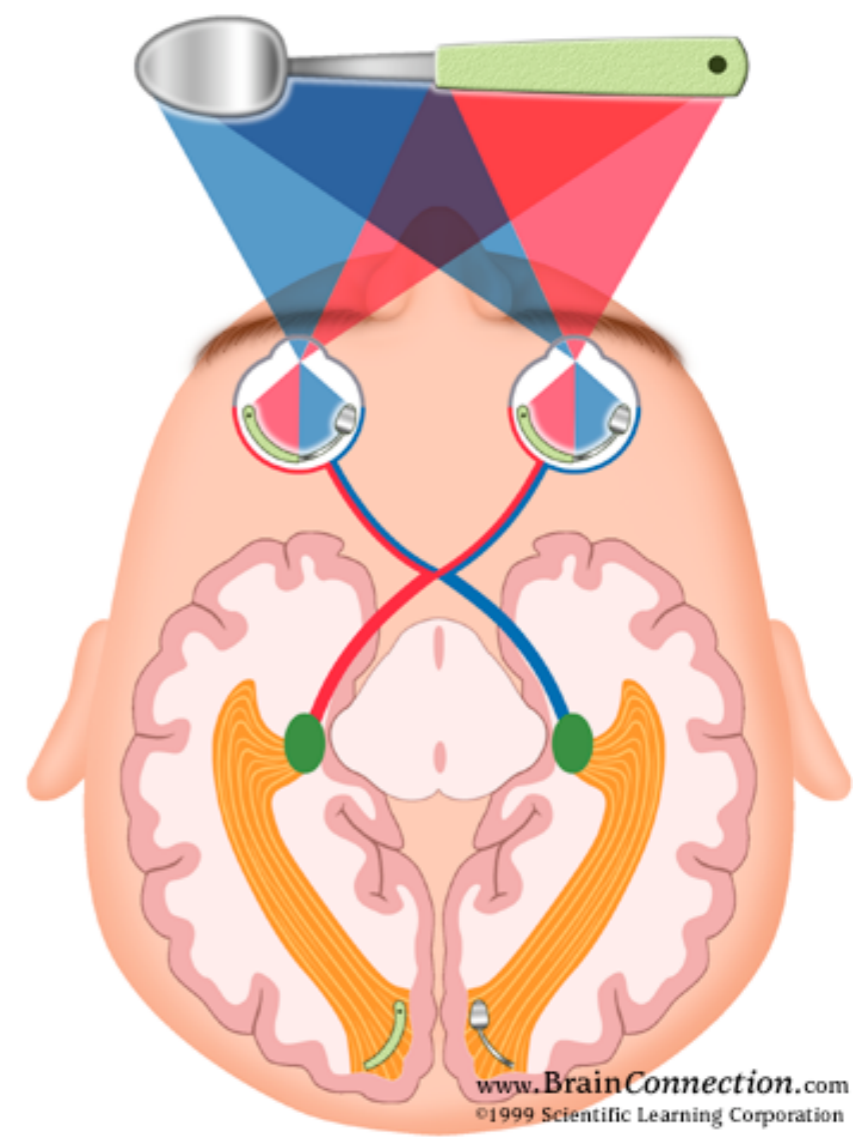
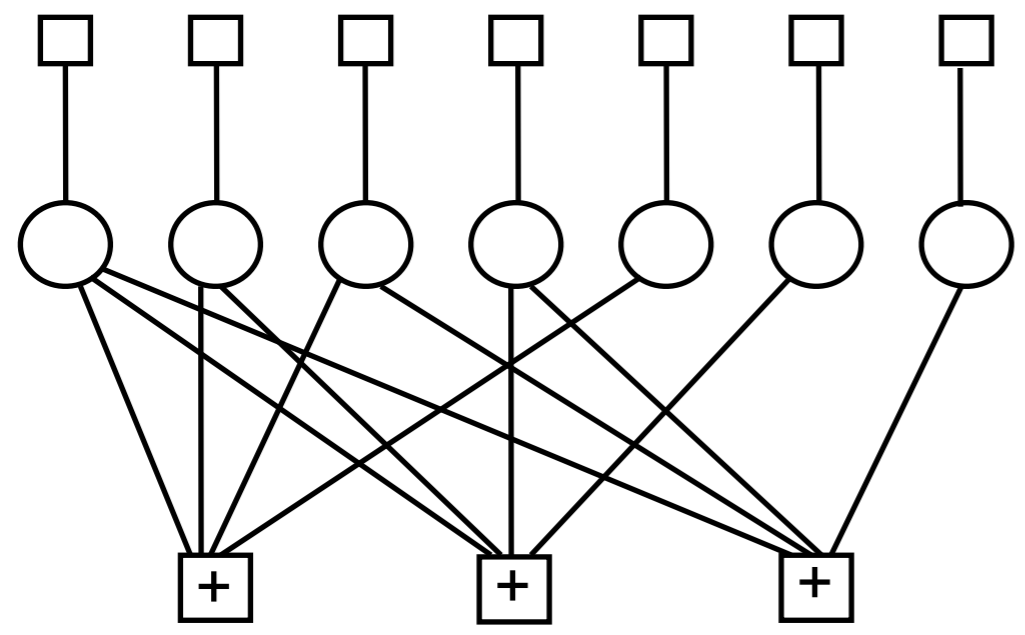
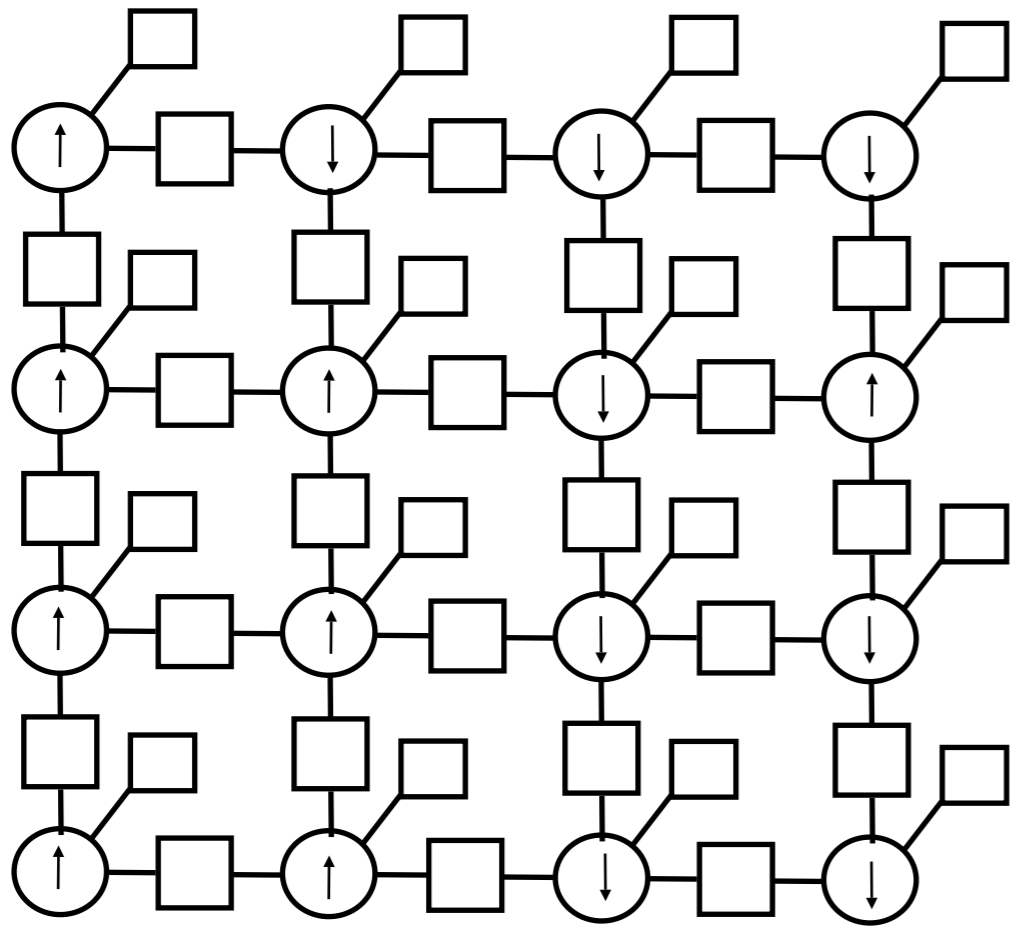


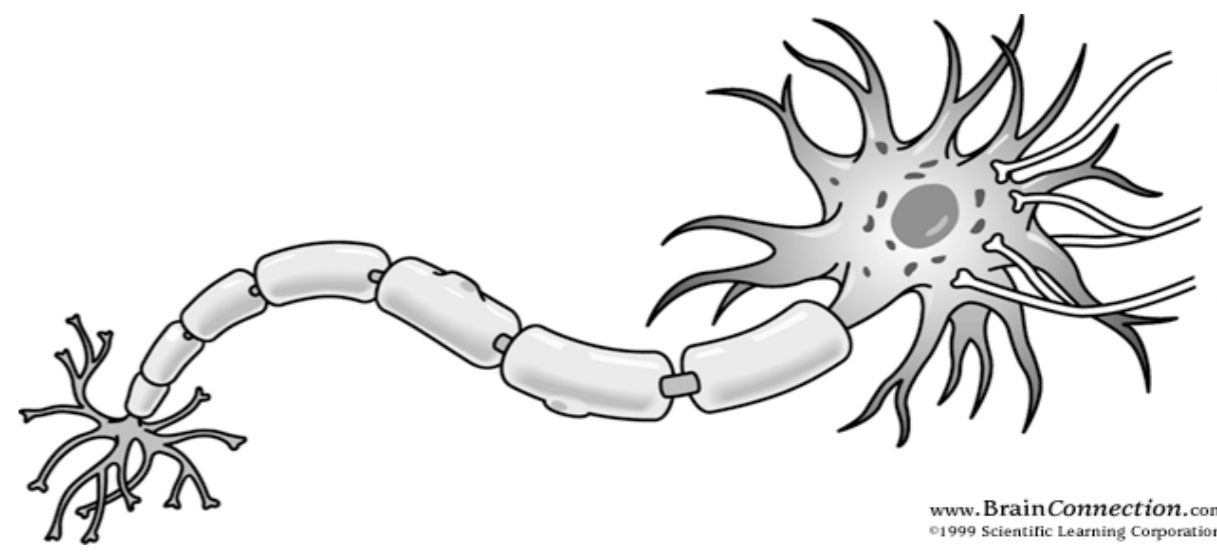
Multi-cellular Logic Circuits

Jonathan Yedidia

Mitsubishi Electric Research Laboratories



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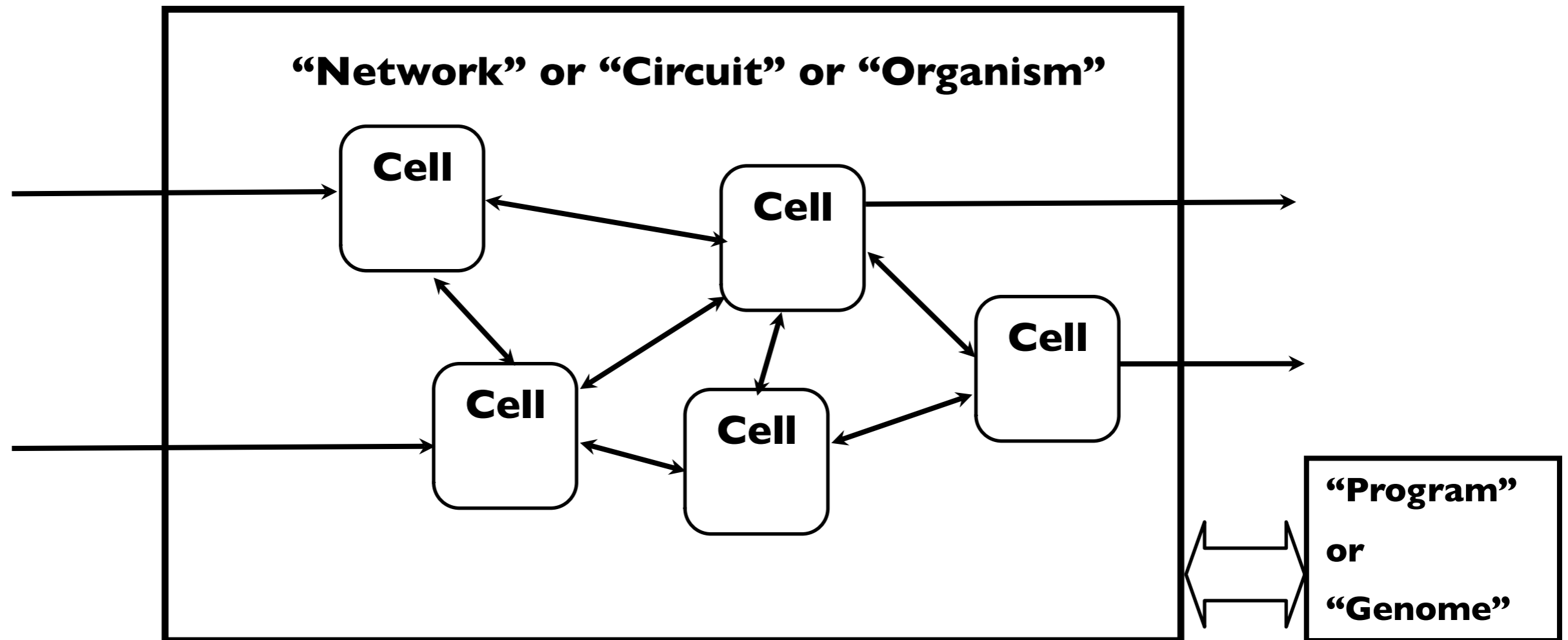


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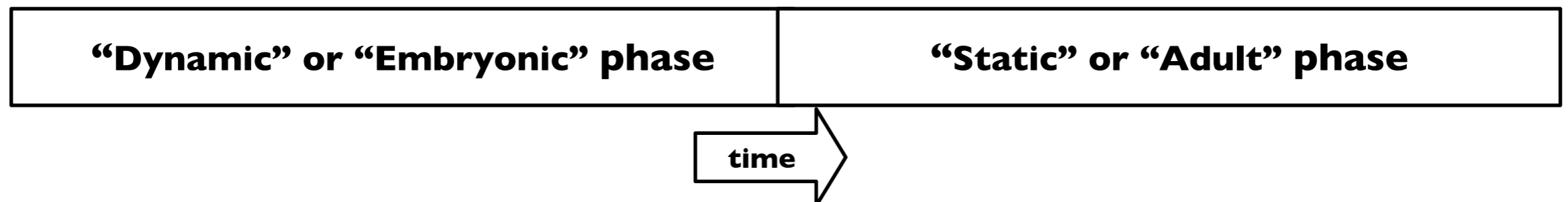
Outline

- A model of the logic of multi-cellular organisms
- Example of the design strategy: a RAM circuit
- Discussion and future prospects
- Biology field trip

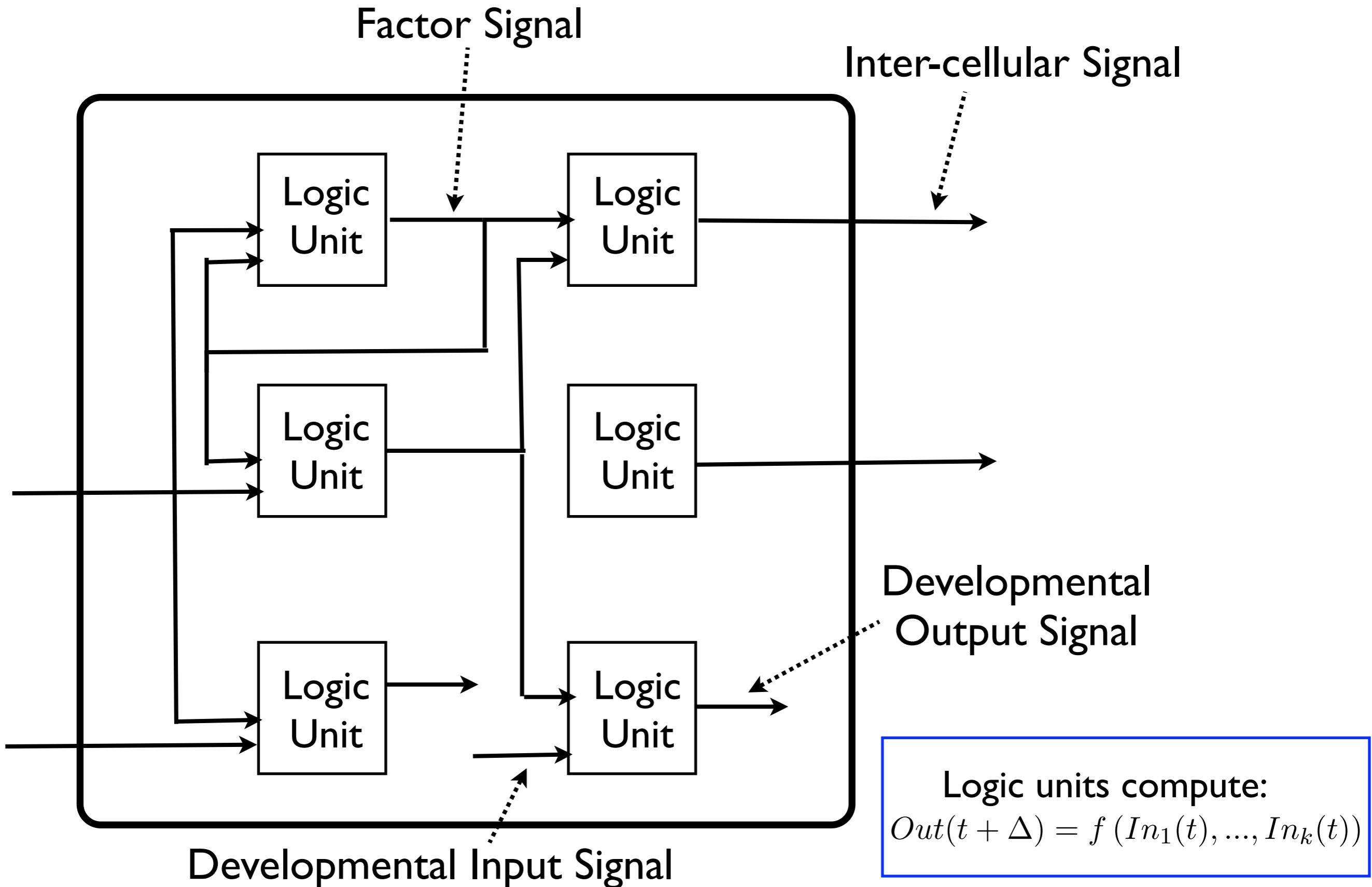
A Simple Model



Key point: all cells have identical specifications

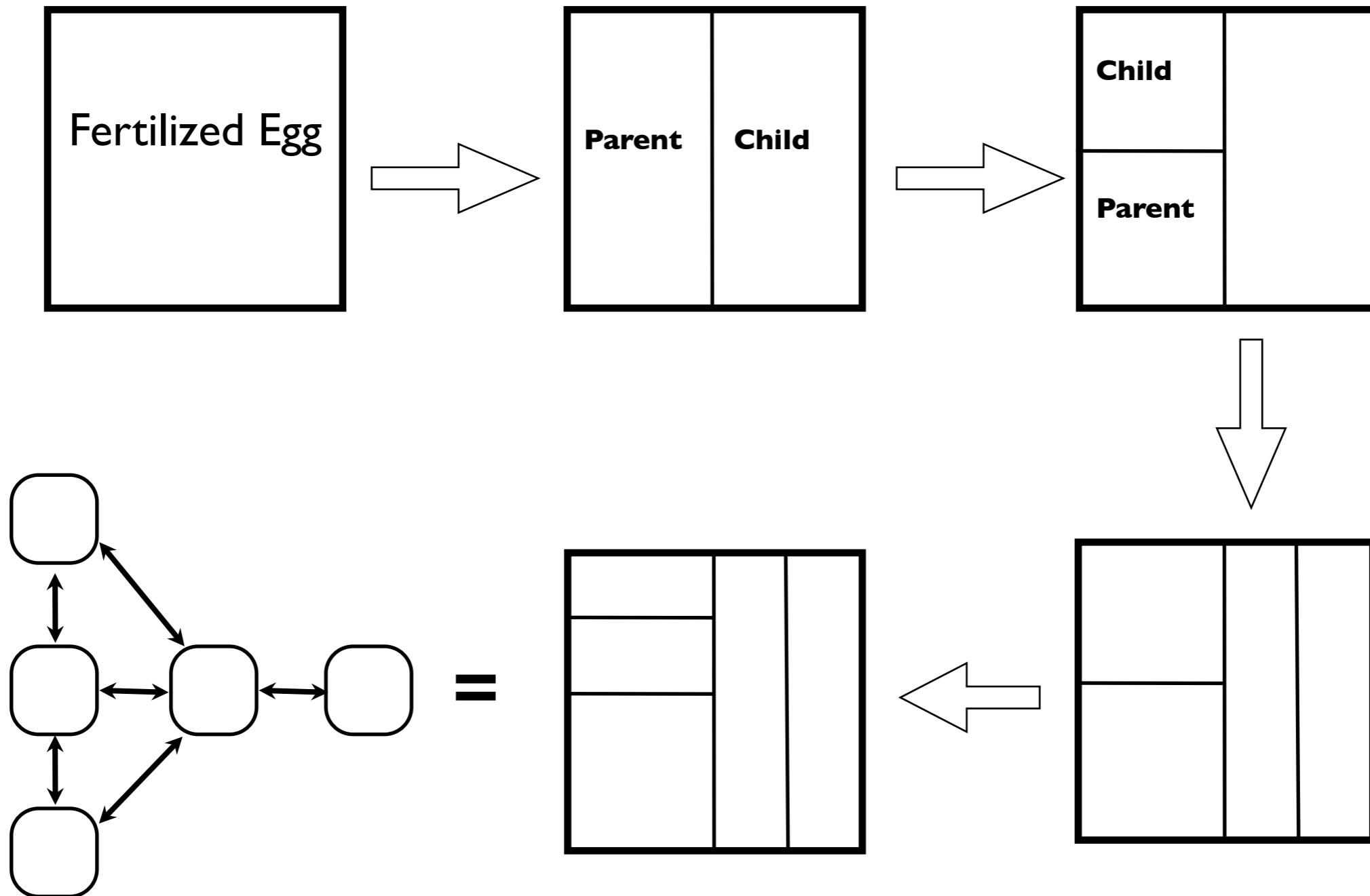


Inside a Cell

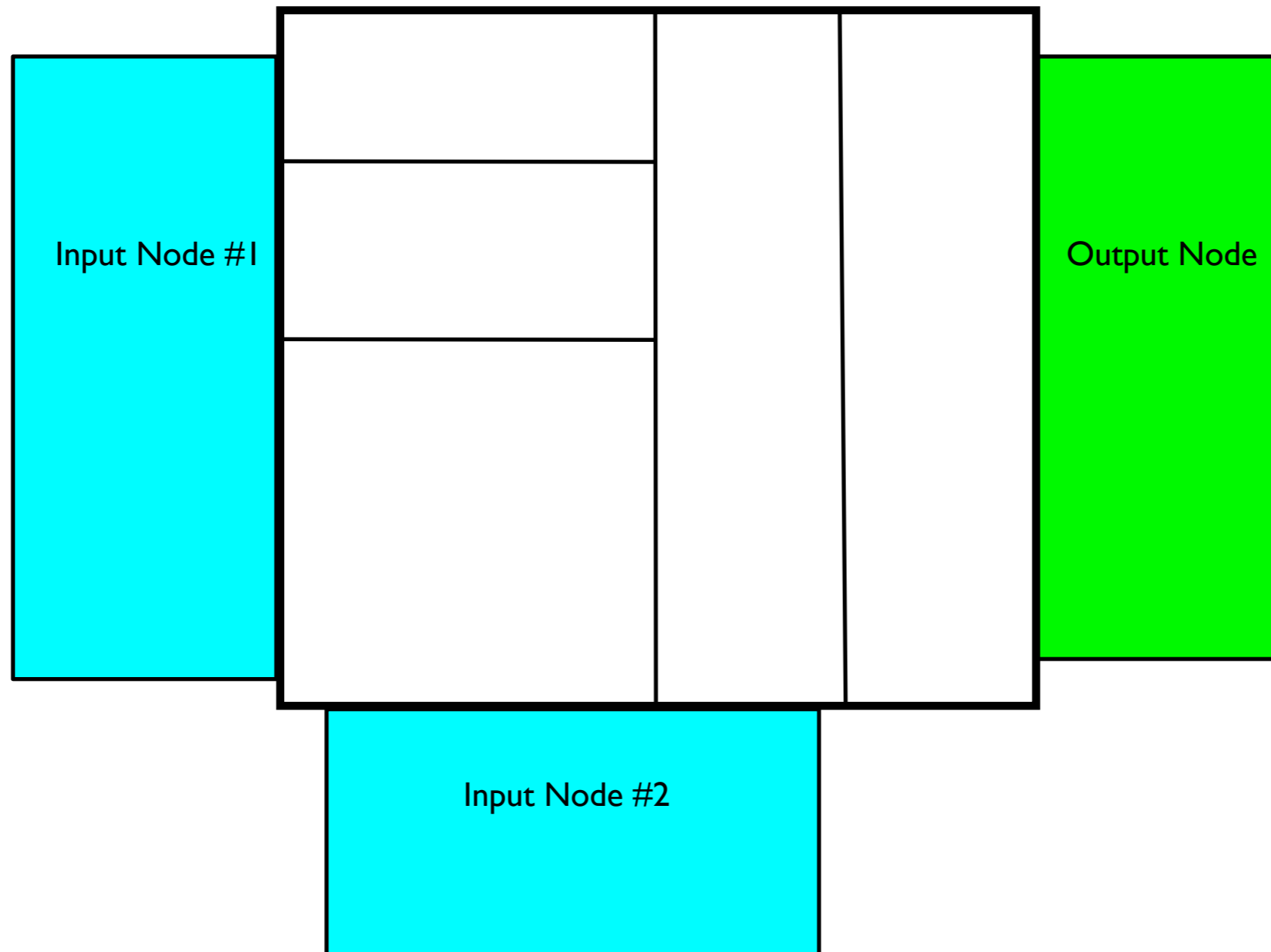


Developmental Phase

Cell Divisions Triggered by "Developmental Output Signals"



Testing the Adult Circuit



More Details and Embellishments

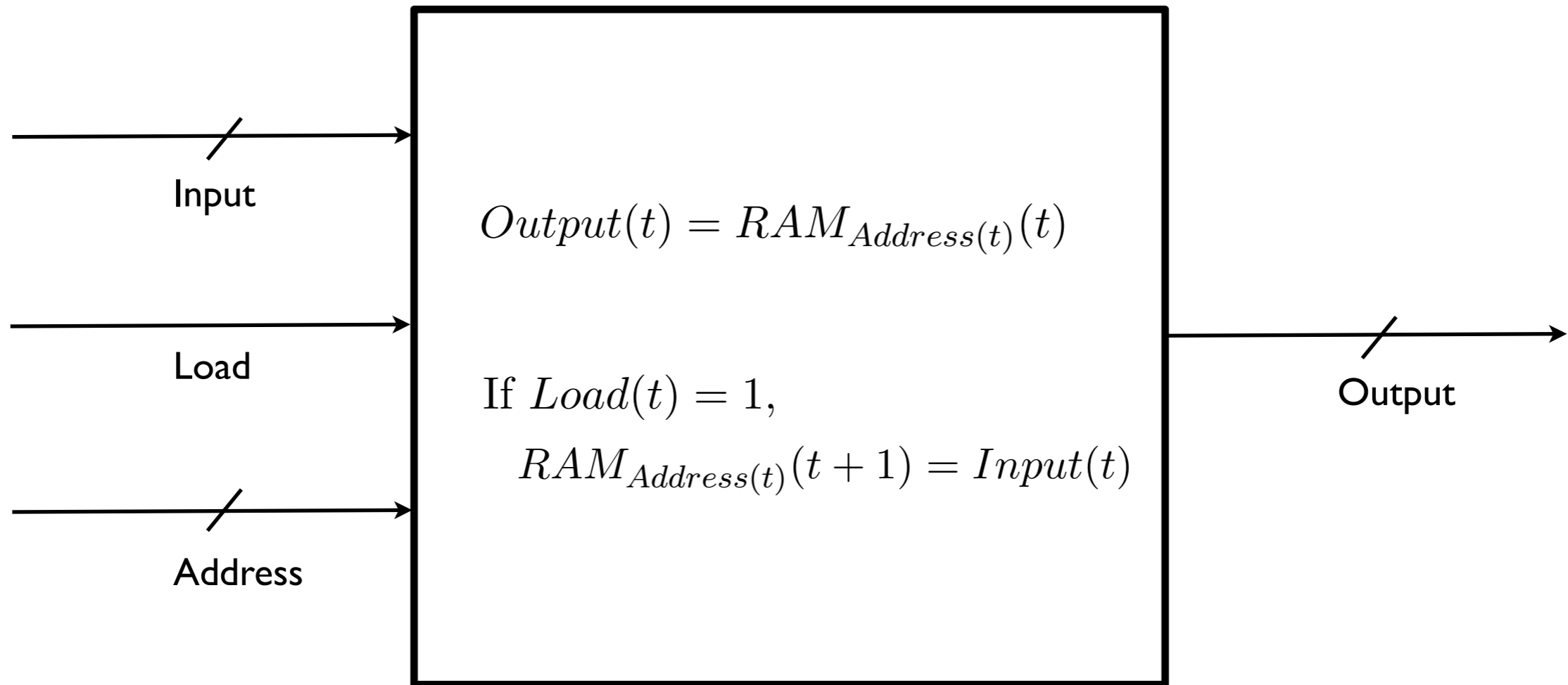
- Reconciliation Functions: If a two or more logic units produce the same output signal, or if a cell receives the same inter-cellular signal from two or more neighboring cells, the value of the signals must be reconciled. For binary signals, an OR function is used.
- Digital, analog, or mixed signals can be used. If analog signals are used, it makes sense to keep them in the range $[0, 1]$, and to use soft logic functions like

$$Out(t + \Delta) = f(In_1 + In_2 - In_1 In_2)$$

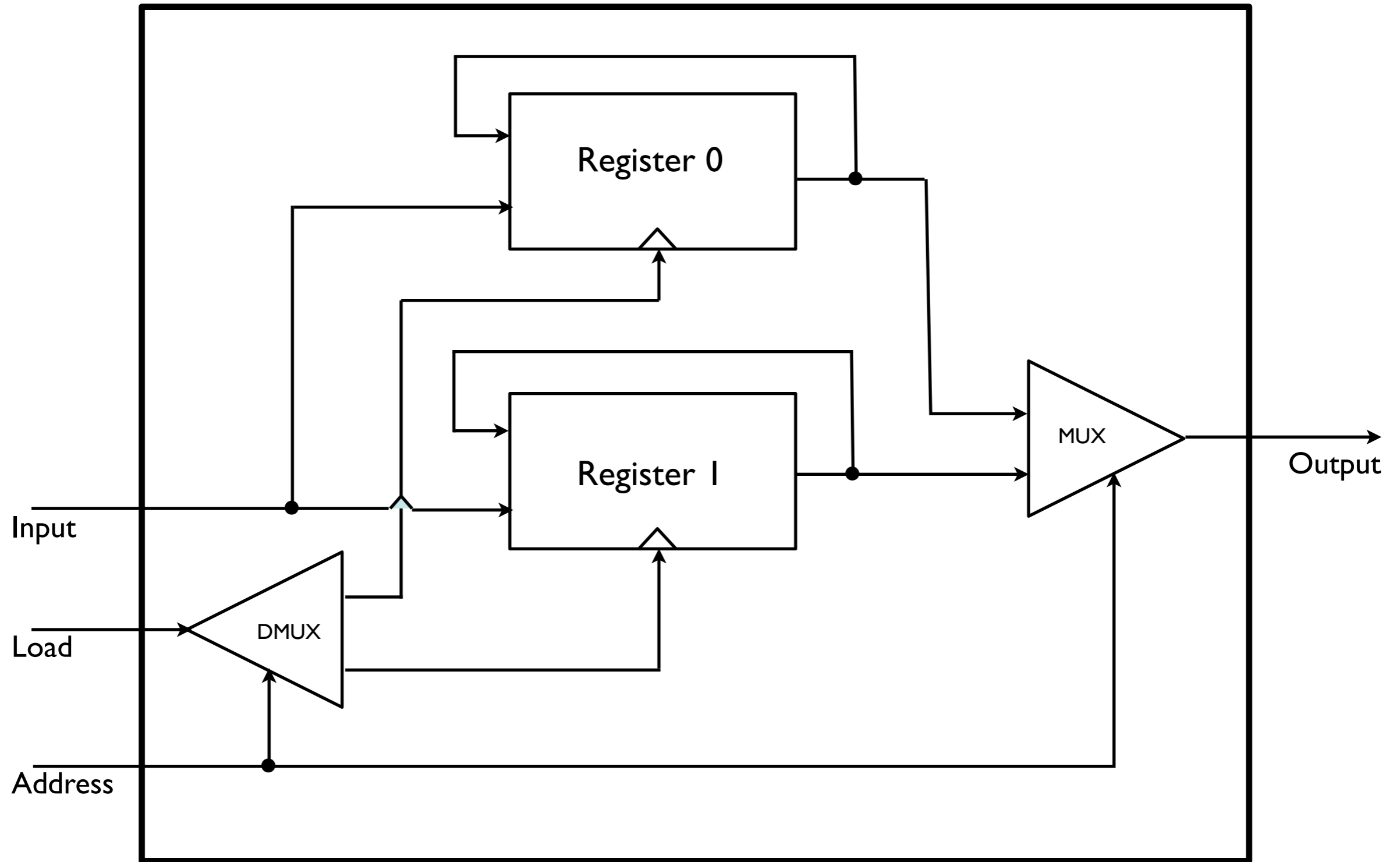
$$f(x) = \frac{x^k}{x^k + (1 - x)^k}$$

- Logic units can be synchronized to a global clock that has discrete time steps; or the cells can be asynchronous, and the logic units could have arbitrary delays.

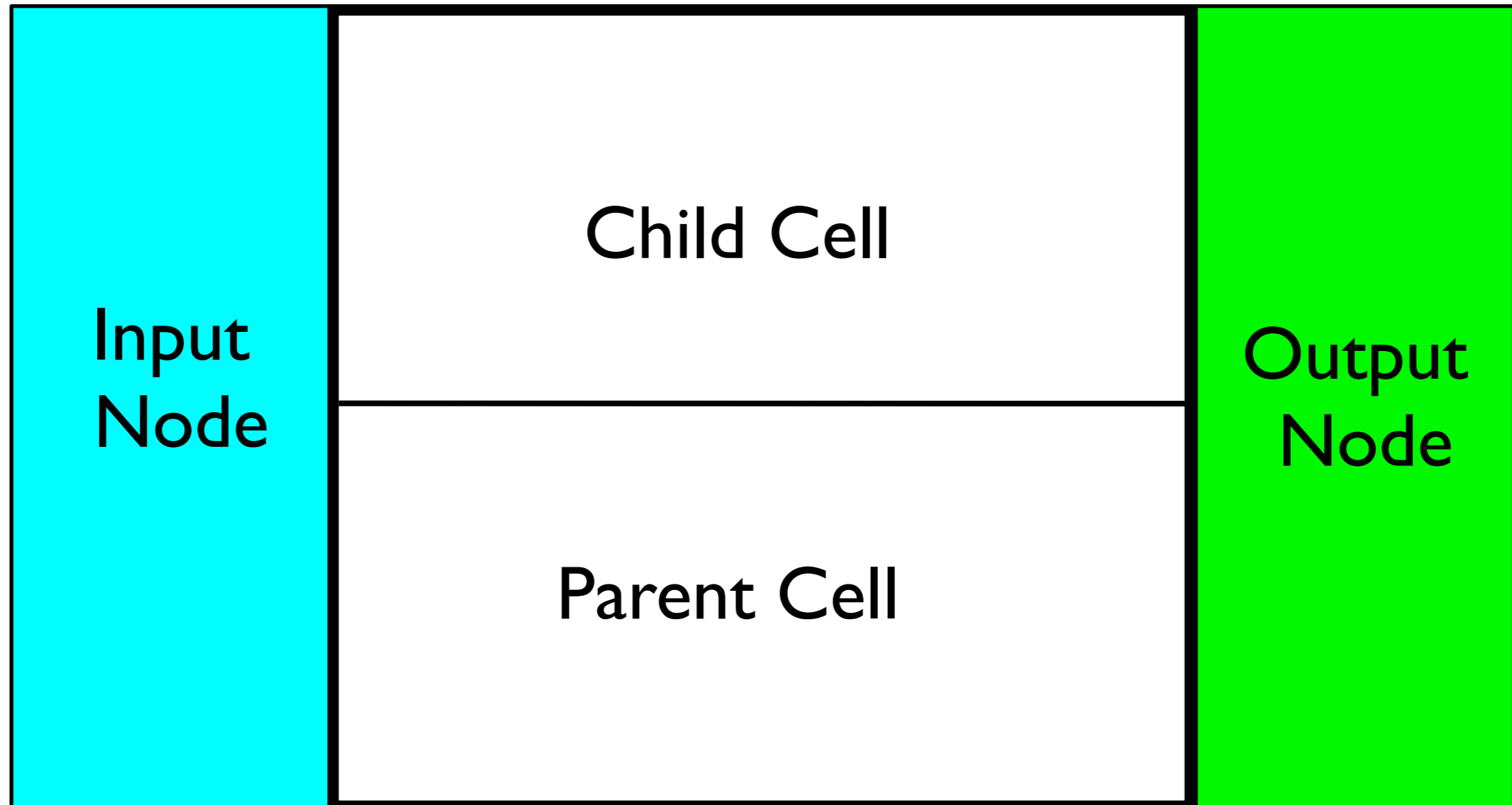
A Random-Access Memory



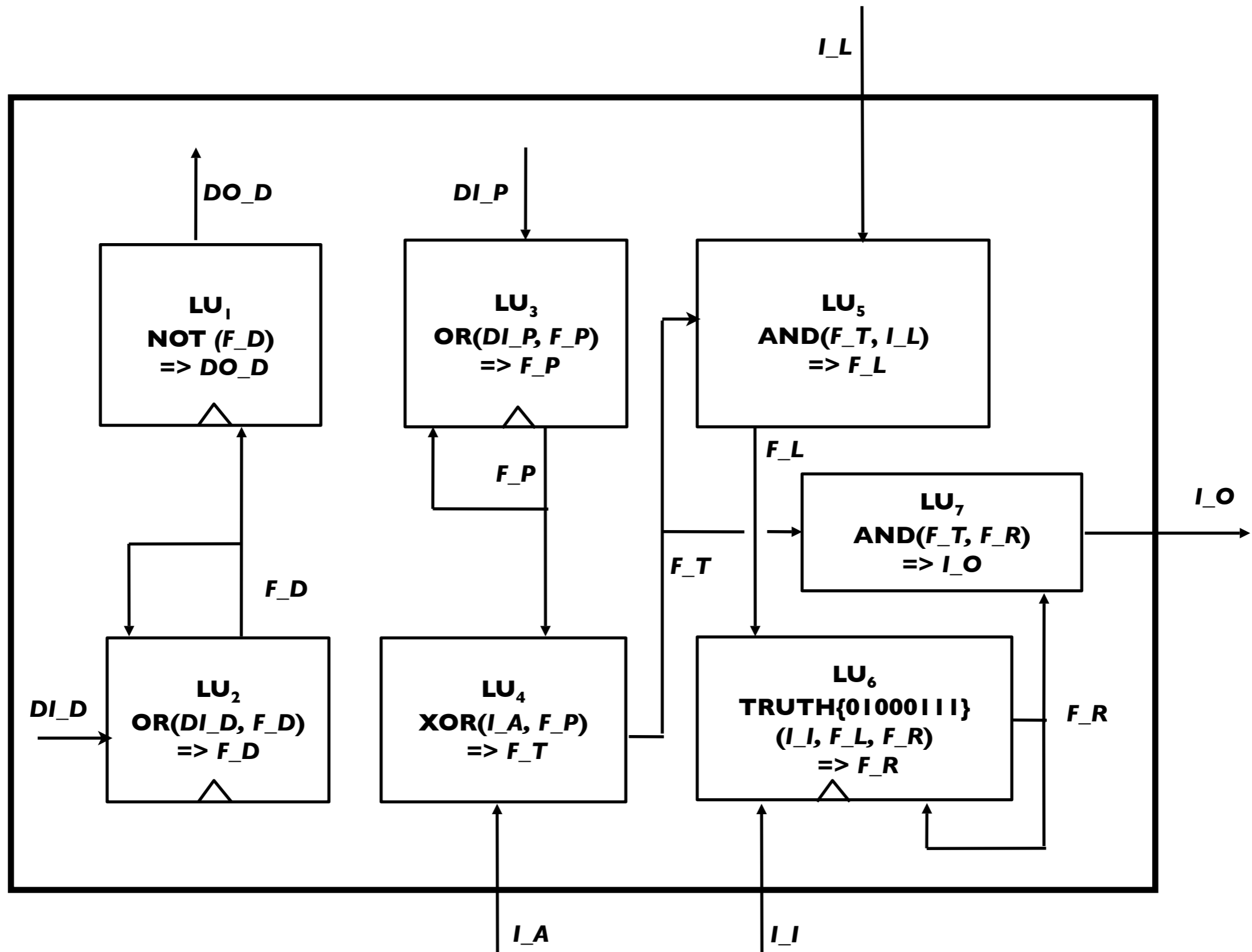
Standard Design (for Tiny-RAM)



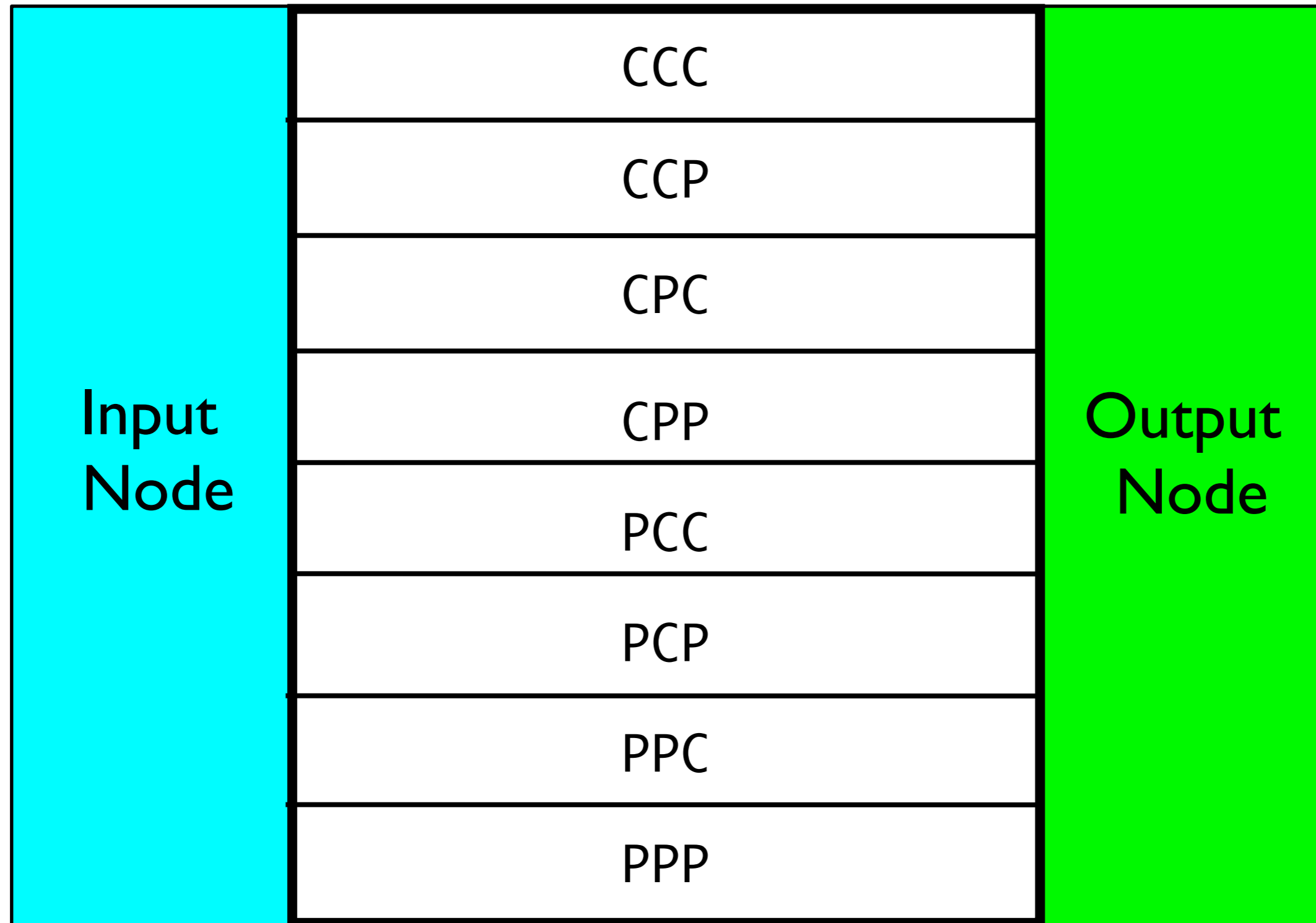
Set-up for Adult Tiny-RAM



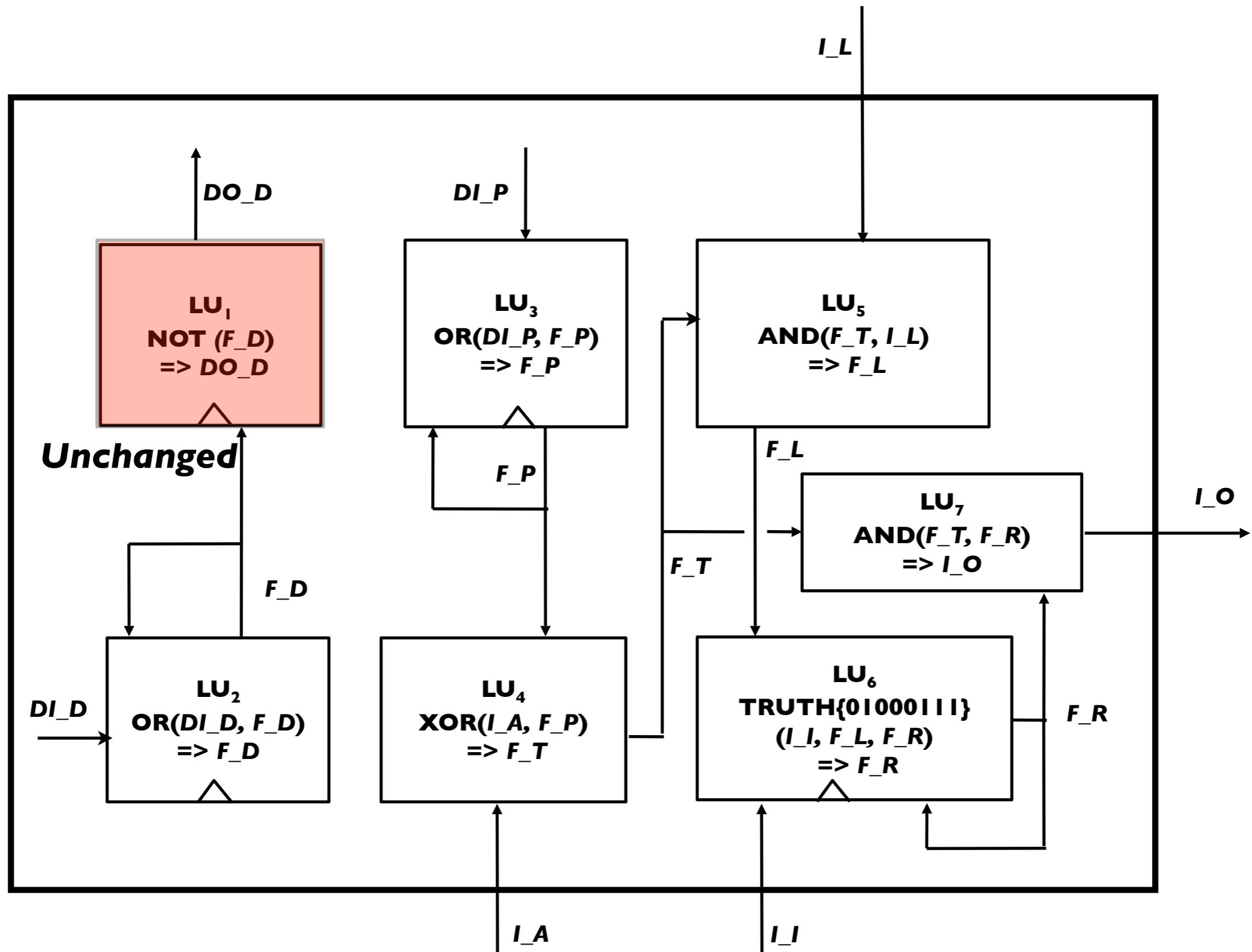
Logic Units in One Tiny-RAM Cell



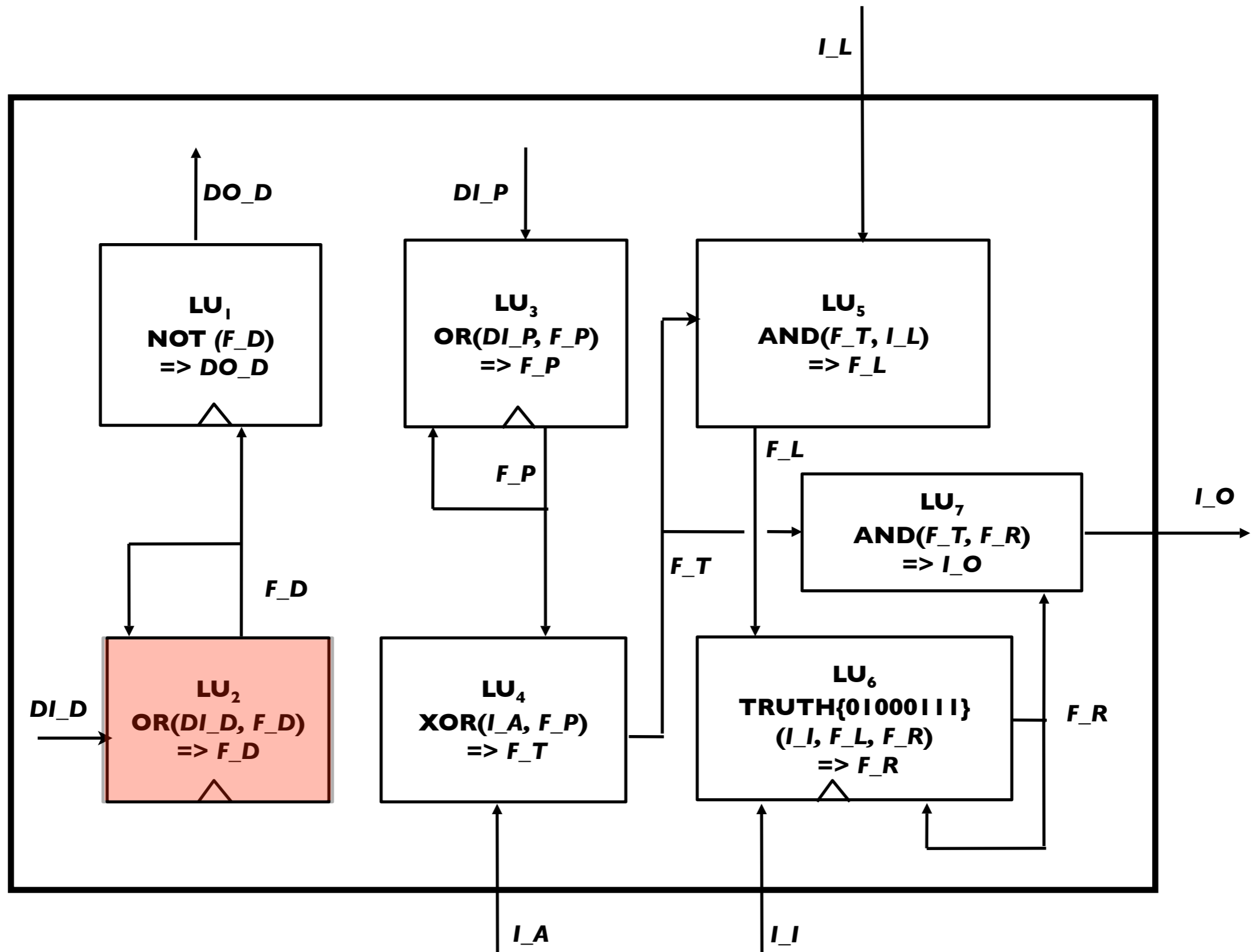
Scaling up the RAM



Scaling Changes



Scaling Changes

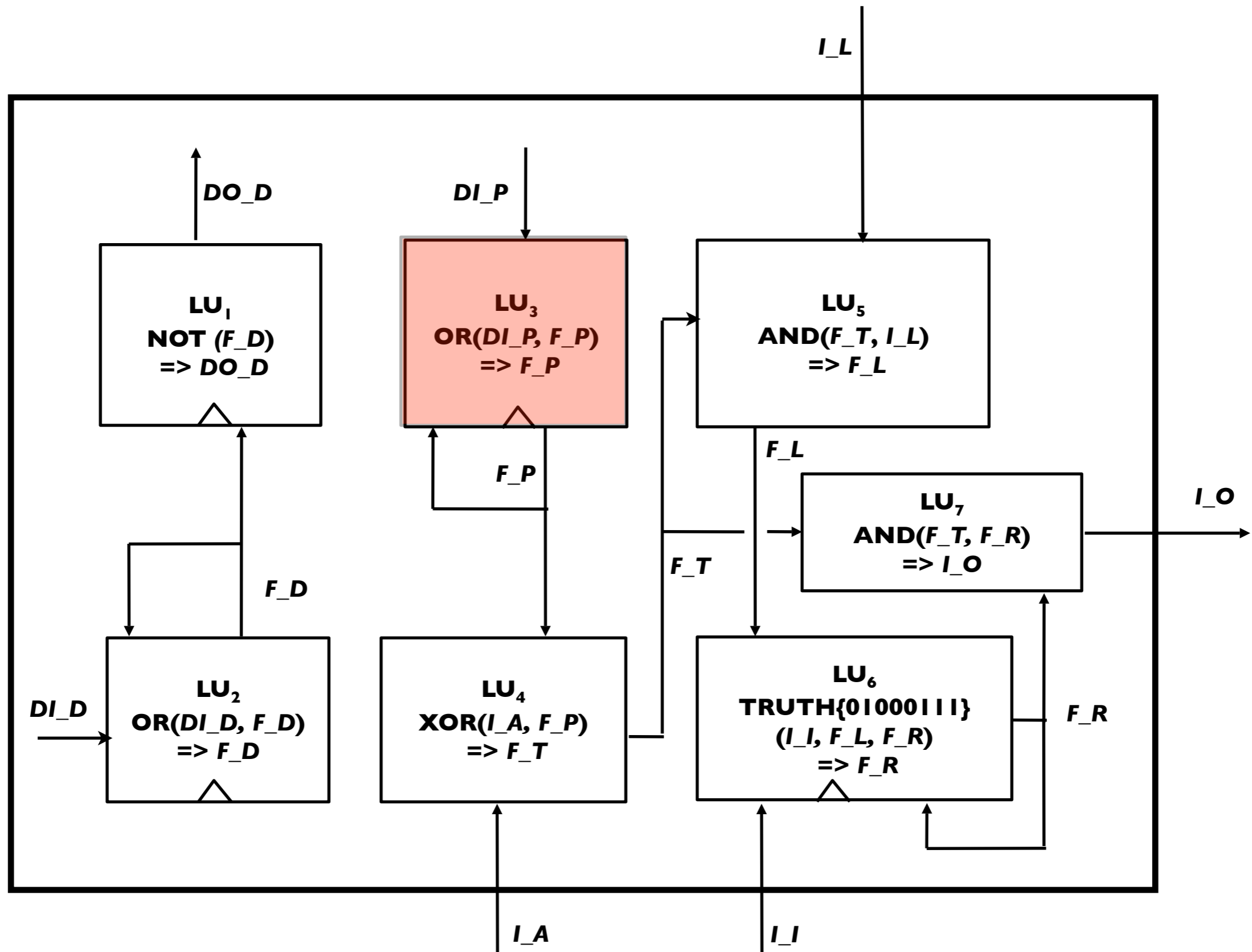


LU2: $\text{Or}(\text{DI_D}, \text{F_D}) \Rightarrow \text{F_D}$

replaced with

- $\text{Or}(\text{DI_D}, \text{F_DI}) \Rightarrow \text{F_DI}$
- $\text{Or}(\text{And}(\text{DI_D}, \text{F_DI}), \text{F_D2}) \Rightarrow \text{F_D2}$
- ...
- $\text{Or}(\text{And}(\text{DI_D}, \text{F_D}[K-1]), \text{F_D}) \Rightarrow \text{F_D}$

Scaling Changes

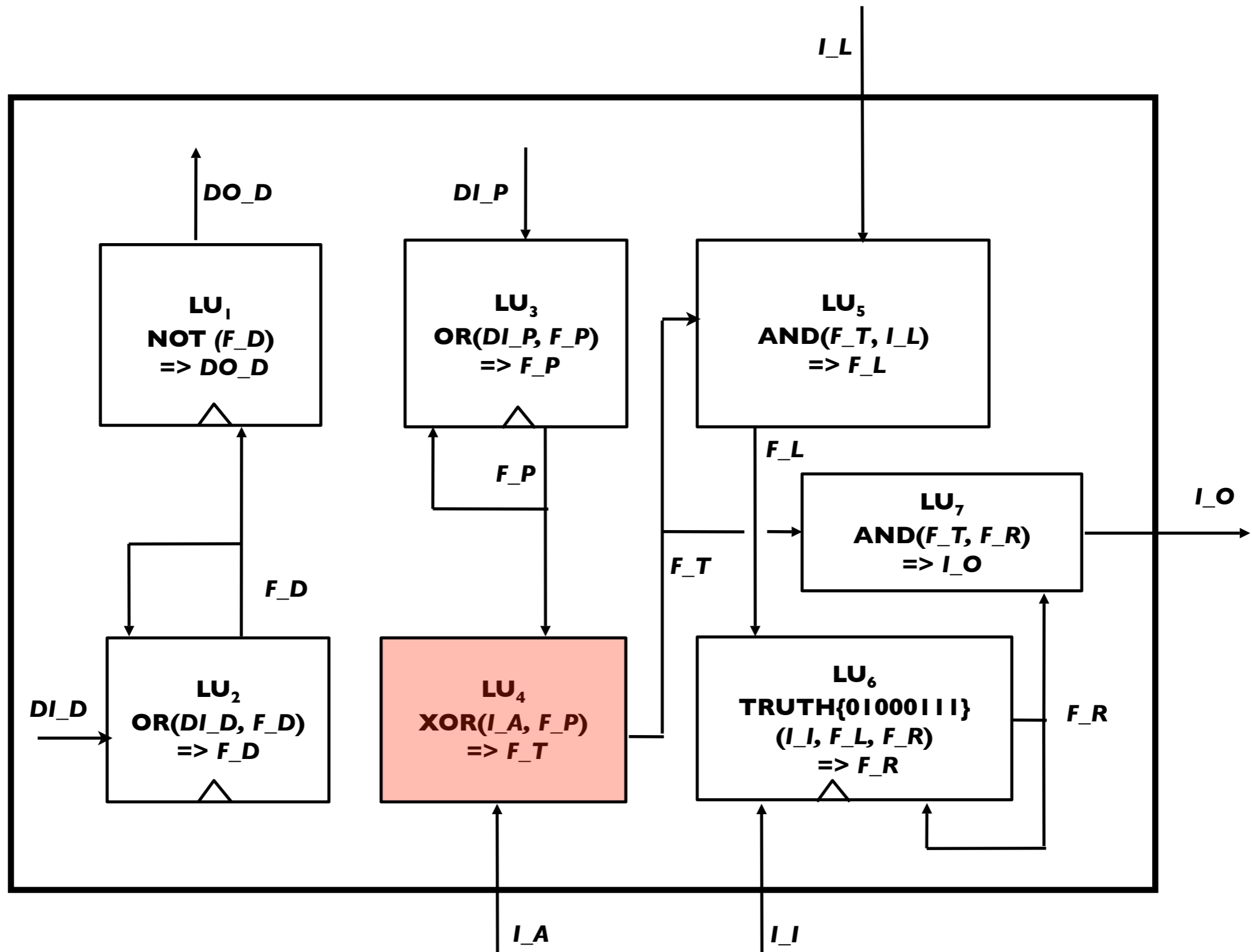


LU3: $\text{Or}(\text{DI_P}, \text{F_P}) \Rightarrow \text{F_P}$

replaced with

- $\text{Or}(\text{And}(\text{DI_P}, \text{Not}(\text{F_D1})), \text{F_P1}) \Rightarrow \text{F_P1}$
- $\text{Or}(\text{And}(\text{DI_P}, \text{F_D1}, \text{Not}(\text{F_D2})), \text{F_P2}) \Rightarrow \text{F_P2}$
-
- $\text{Or}(\text{And}(\text{DI_P}, \text{F_D}[k-1], \text{Not}(\text{F_D})), \text{F_P}[K]) \Rightarrow \text{F_P}[K]$

Scaling Changes



LU4: $XOR(I_A, F_P) \Rightarrow F_T$

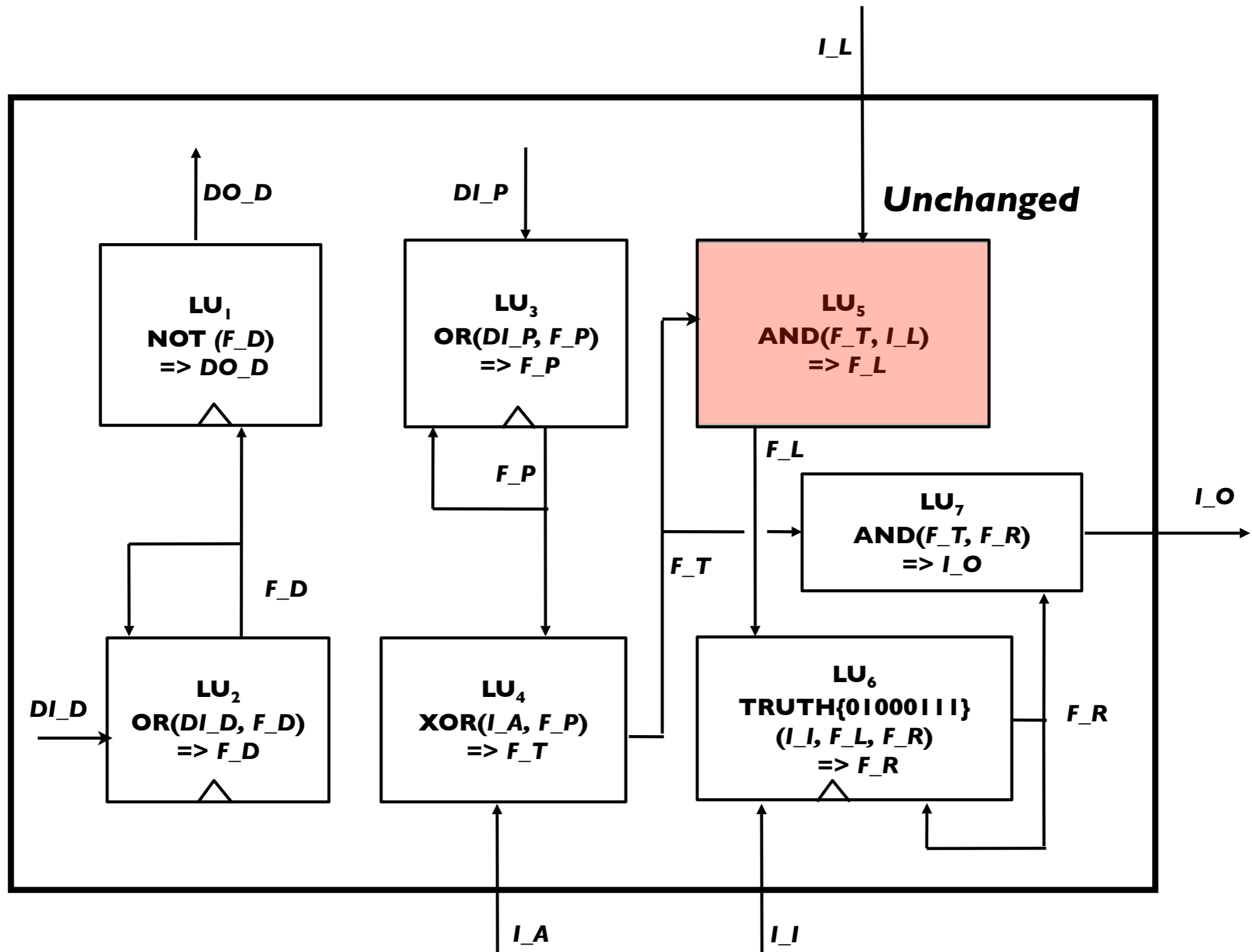
replaced with

- $XOR(I_A1, F_P1) \Rightarrow F_T1$
- $XOR(I_A2, F_P2) \Rightarrow F_T2$
-
- $XOR(I_A[k], F_P[k]) \Rightarrow F_T[K]$

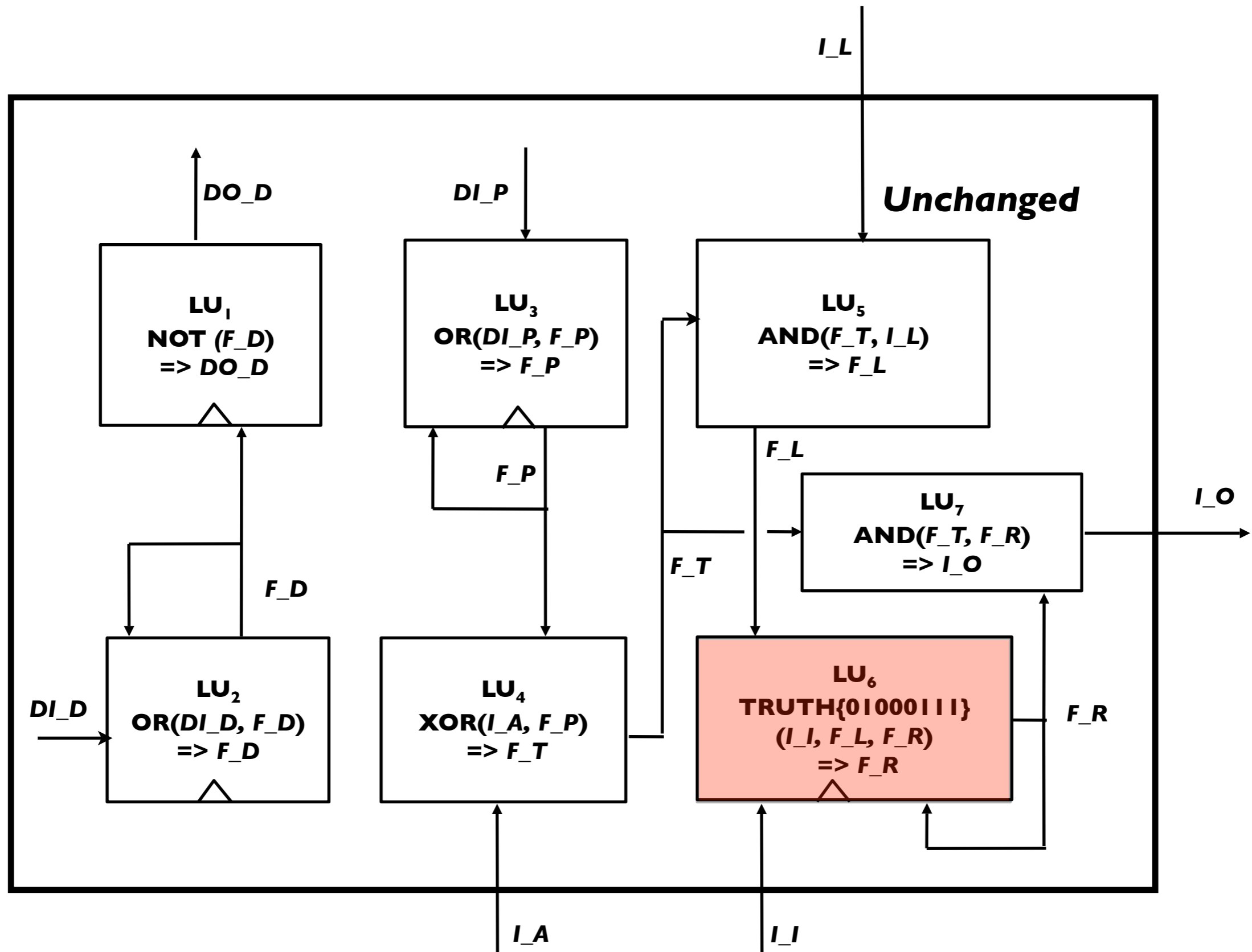
plus

- $And(F_T1, F_T2, \dots, F_T[K]) \Rightarrow F_T$

Scaling Changes



Scaling Changes

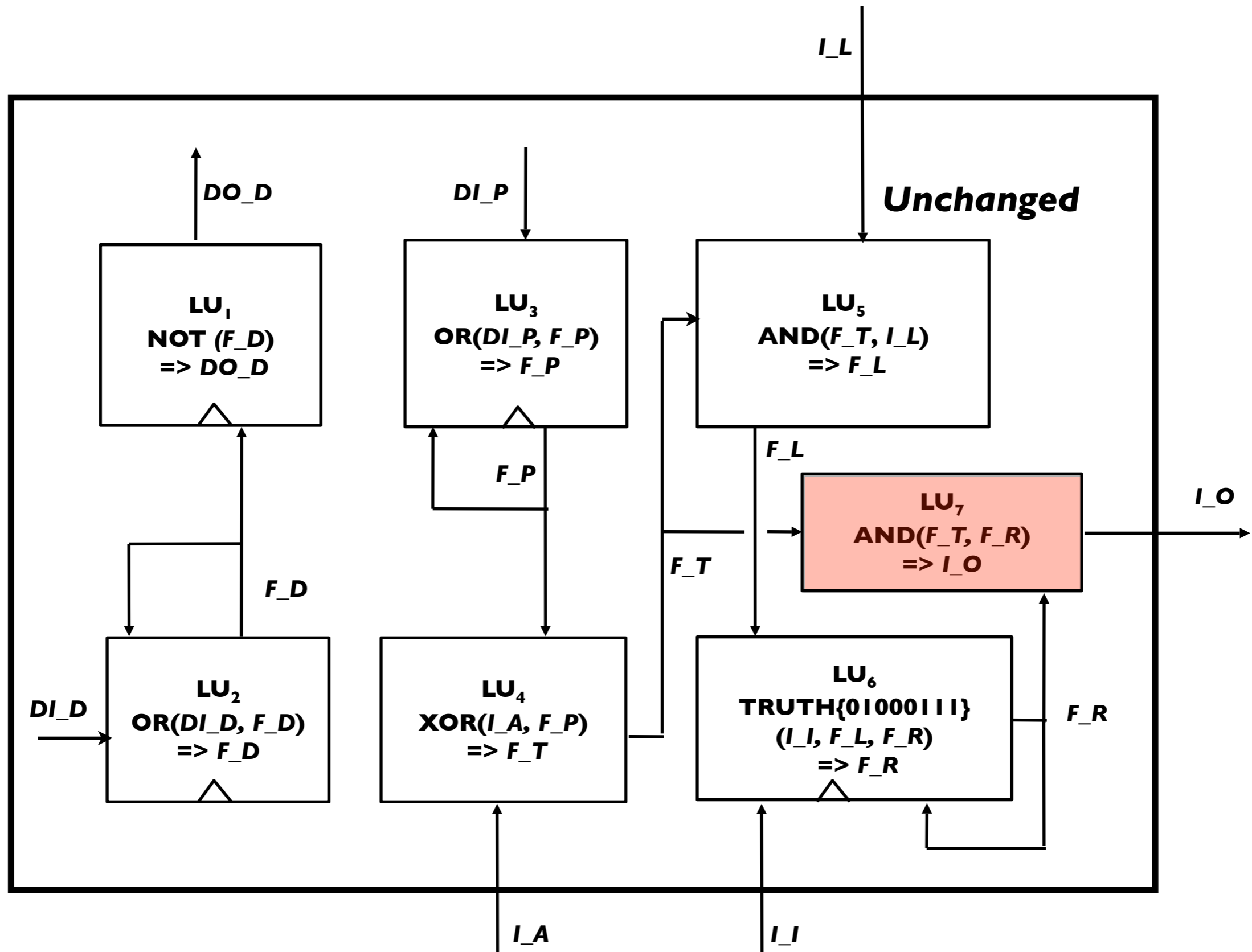


LU6: $\text{TRUTH}\{01000111\}(I_I, F_L, F_R) \Rightarrow F_R$

replaced with

- $\text{TRUTH}\{01000111\}(I_{I1}, F_L, F_{R1}) \Rightarrow F_{R1}$
- $\text{TRUTH}\{01000111\}(I_{I2}, F_L, F_{R2}) \Rightarrow F_{R2}$
-
- $\text{TRUTH}\{01000111\}(I_I[L], F_L, F_R[L]) \Rightarrow F_R[L]$

Scaling Changes



LU7: $\text{And}(F_T, F_R) \Rightarrow I_O$

replaced with

- $\text{And}(F_T, F_R1) \Rightarrow I_O1$
- $\text{And}(F_T, F_R2) \Rightarrow I_O2$
-
- $\text{And}(F_T, F_R[L]) \Rightarrow I_O[L]$

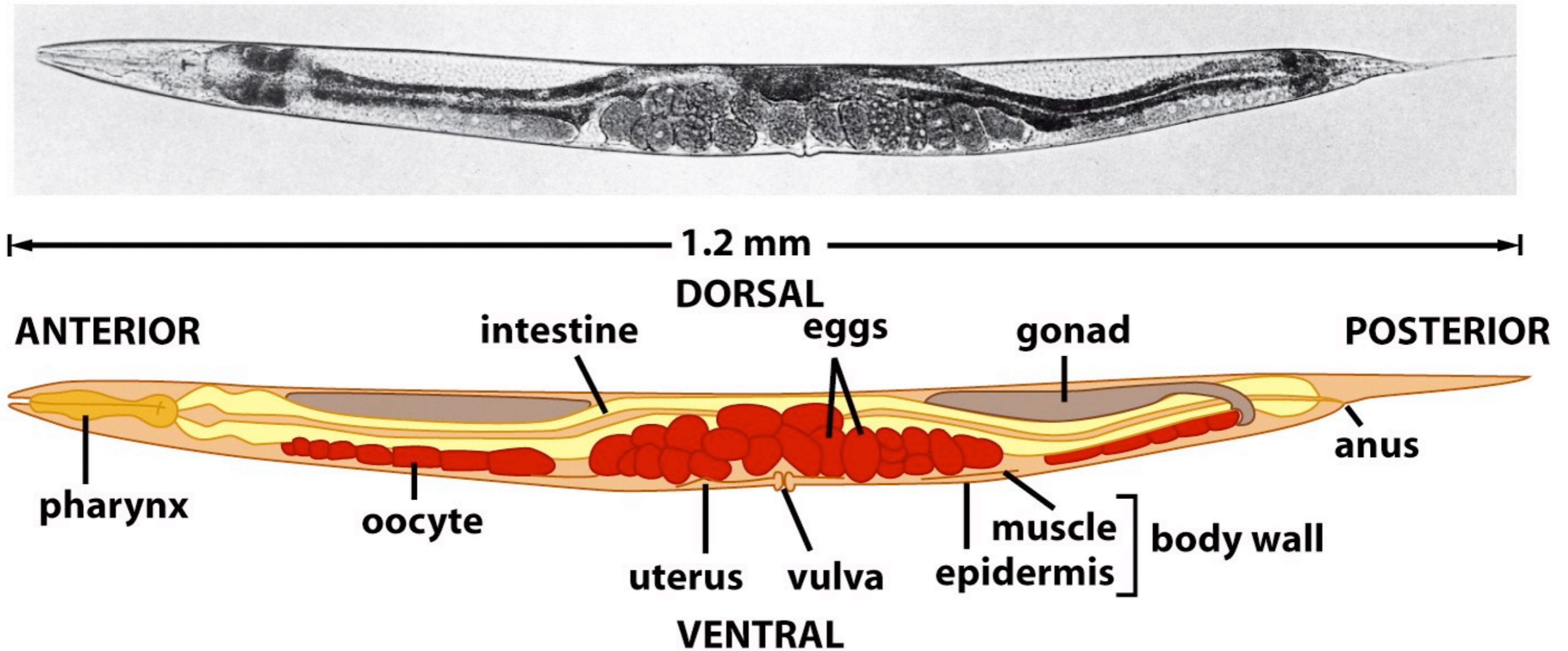
Advantages of multi-cellular logic circuits

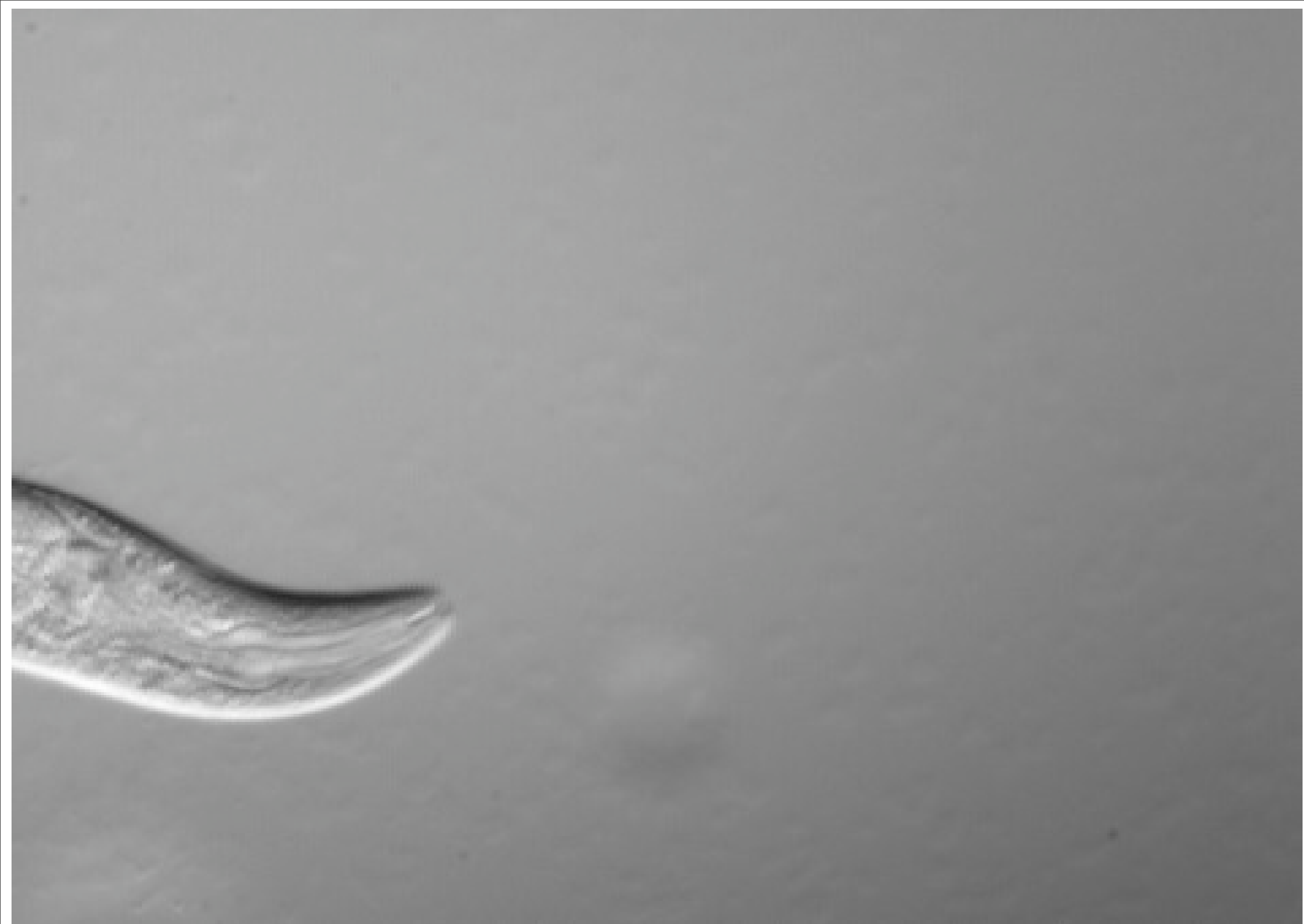
- Can compactly specify a very large network
- Automatic code re-use
- Potentially convenient for mass-production
- Perhaps a compact specification is nice for genetic algorithms, or other blind search strategies.
- Using many cells with identical specifications seems to be a key part of nature's design strategy for building complex machines.

Future Directions

- Evolve multi-cellular logic circuits
- Design/Evolve more complex circuits (e.g. a CPU)
- Evolve circuits that perform inference
- All sorts of “biological” modeling possibilities: “mating” circuits, an embryo circuit developing inside a “mother” circuit, etc.
- Multi-cellular organisms with physical structure: add motors and springs.

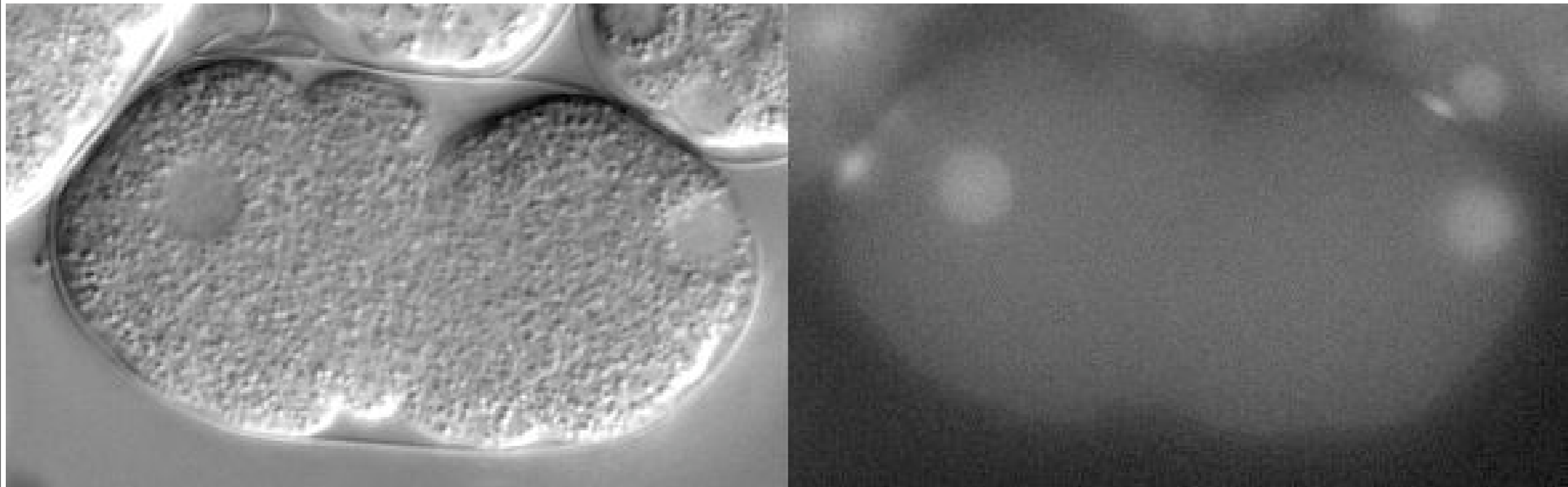
C. elegans: a favorite multi-cellular “model organism”





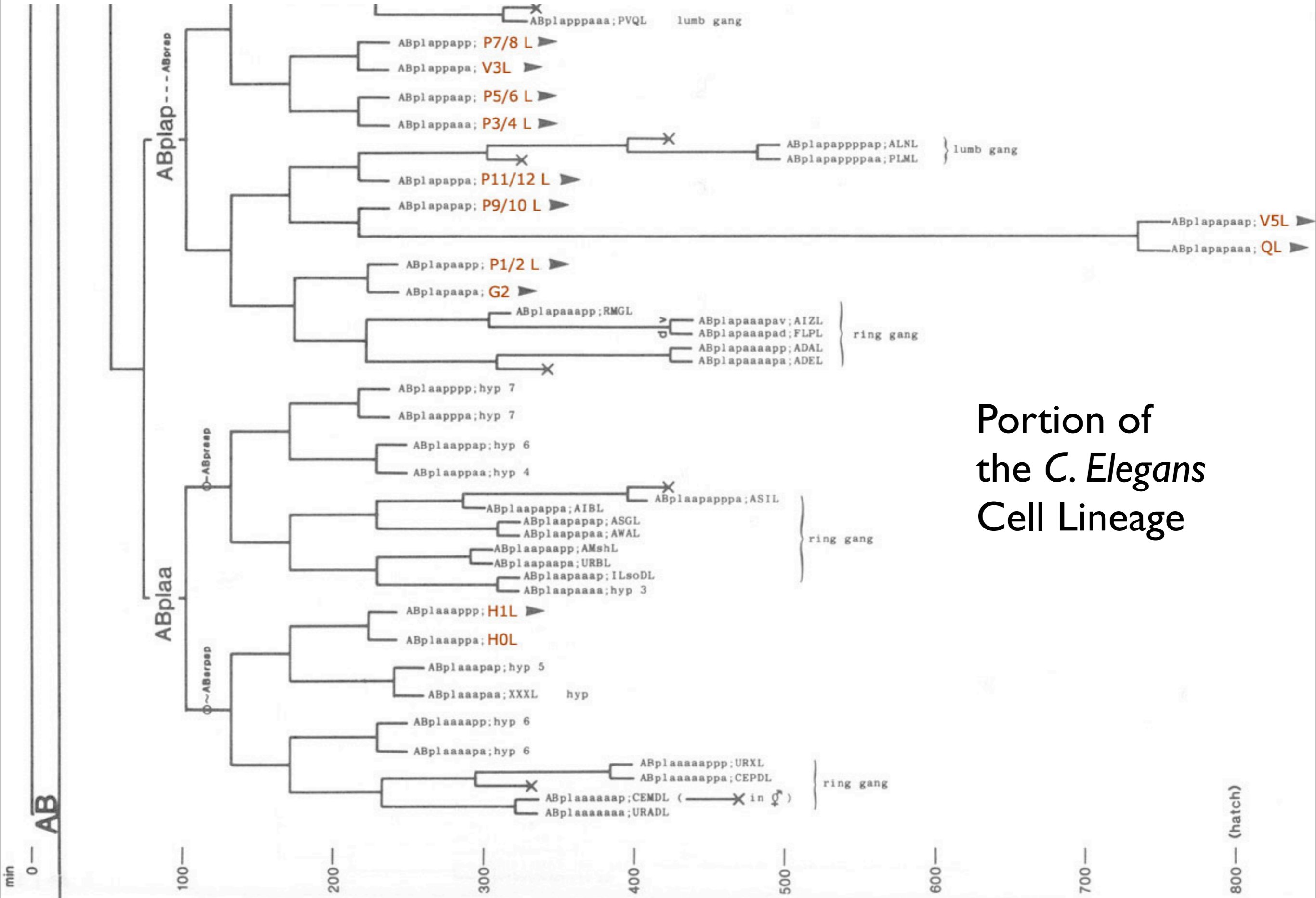
from B. Goldstein lab, U.N.C.

First Stages of Embryonic Development



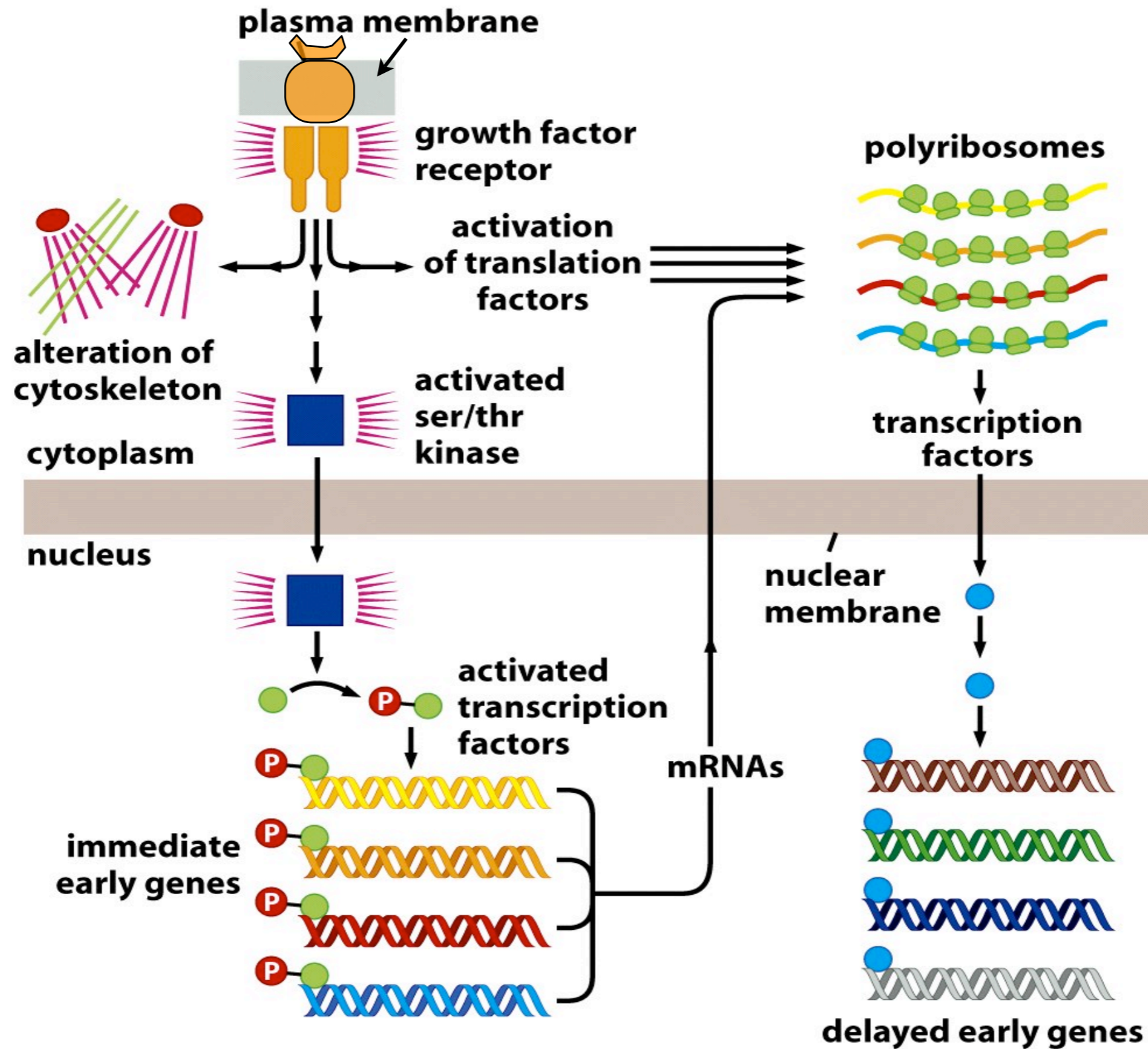
Complete Embryonic Development



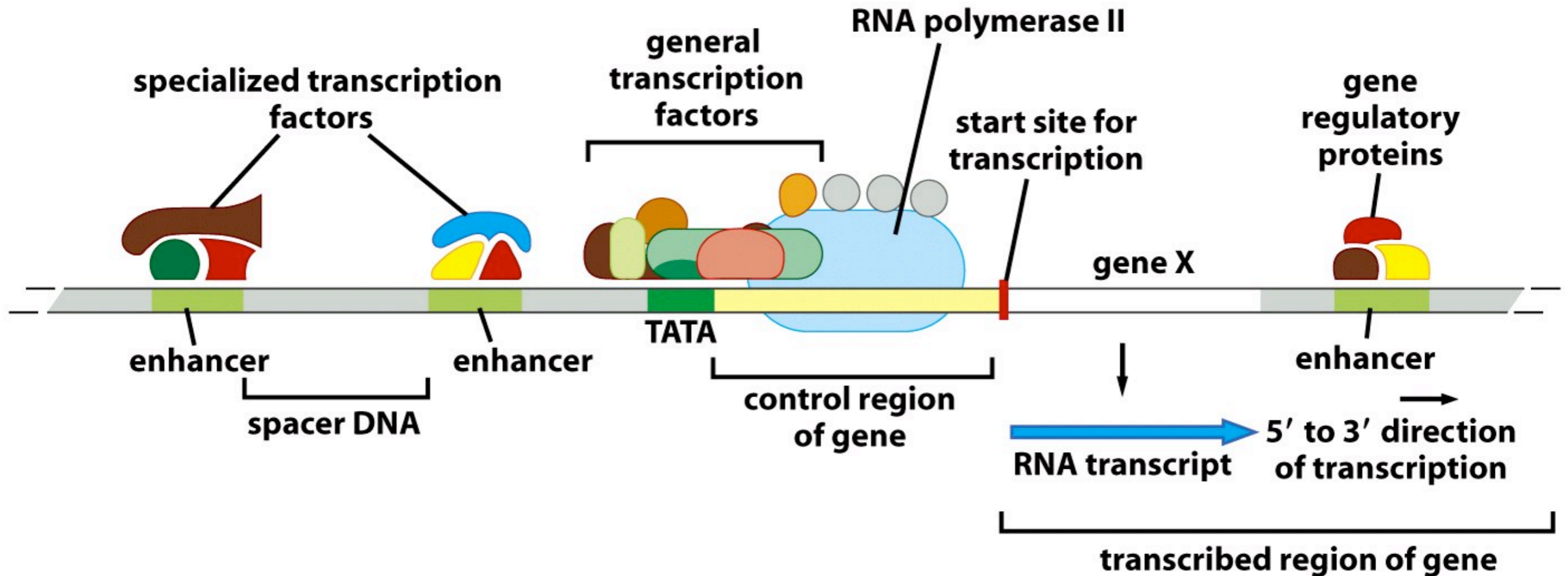


Portion of the *C. Elegans* Cell Lineage

Intra-cellular Signals



Transcription Control



Biological Signal Processing

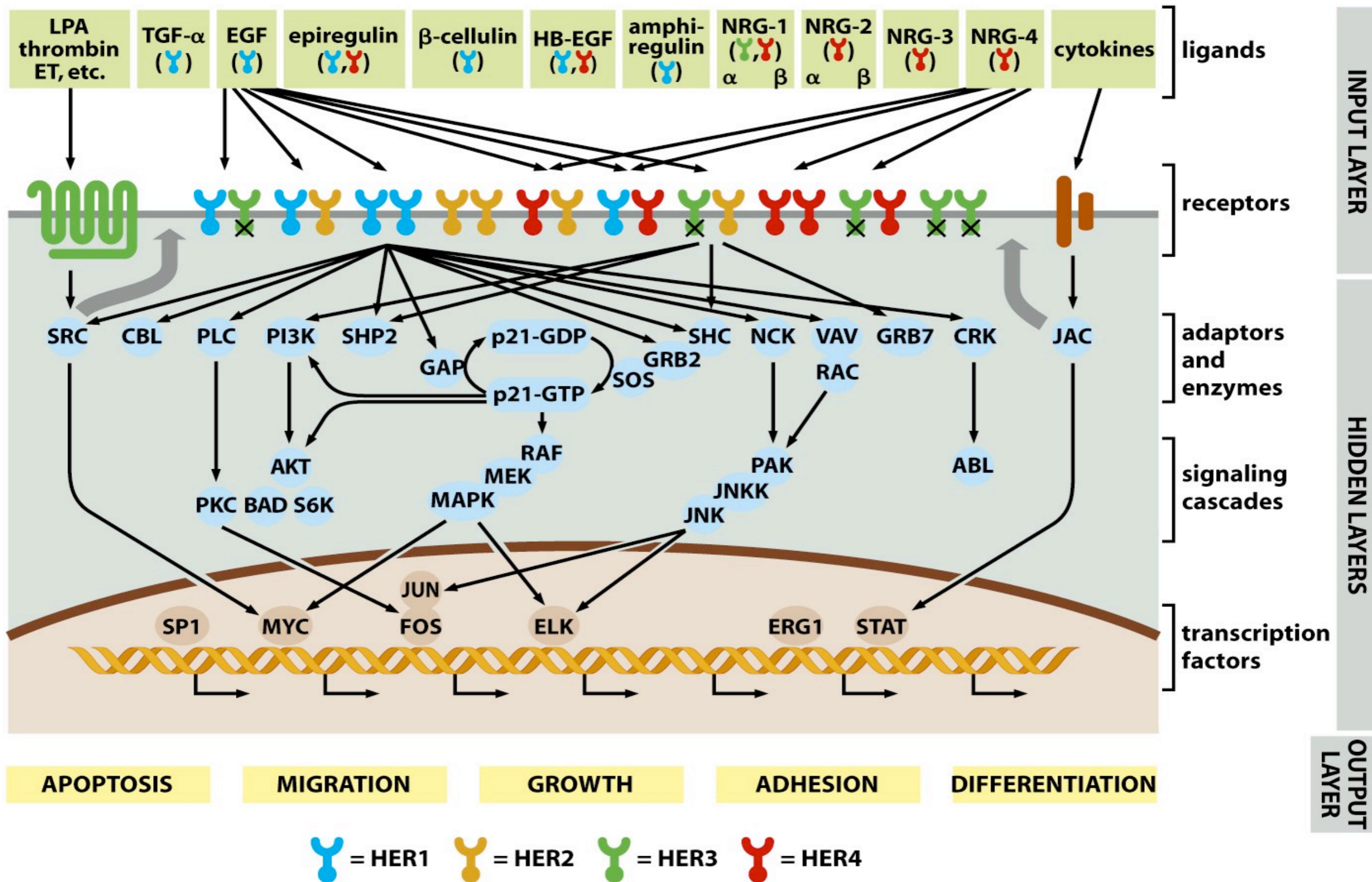
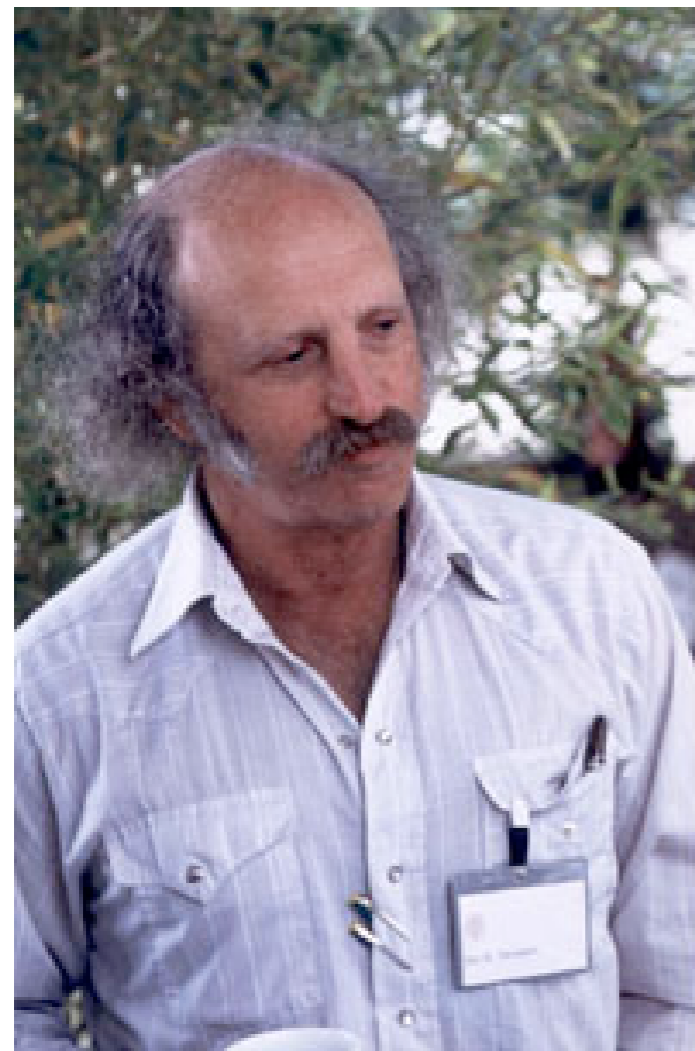


Figure 5.1 *The Biology of Cancer* (© Garland Science 2007) R. Weinberg



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THE REGULATORY GENOME

Gene Regulatory Networks
In Development and Evolution

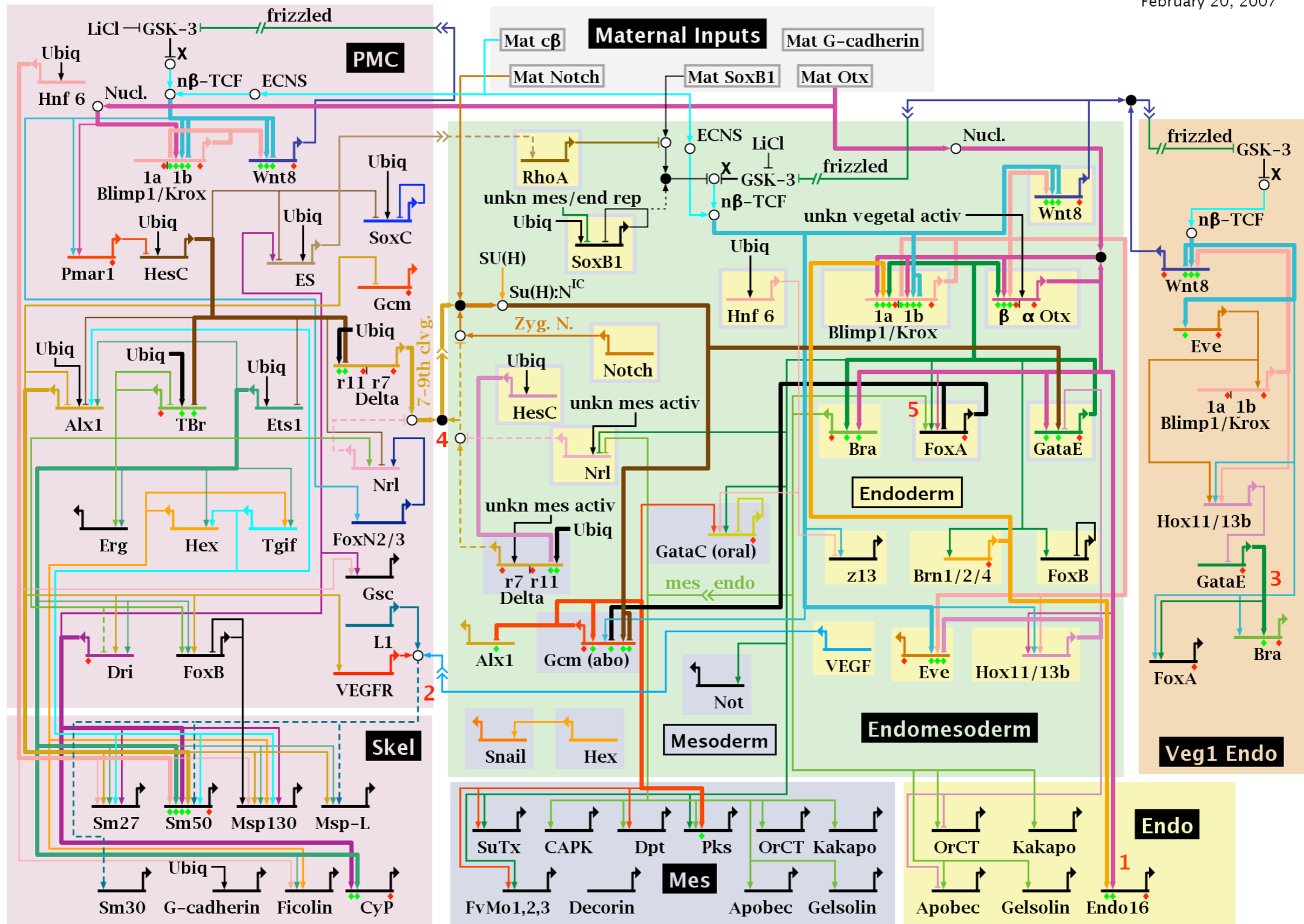
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ERIC H. DAVIDSON
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Endomesoderm Specification to 30 Hours

February 20, 2007

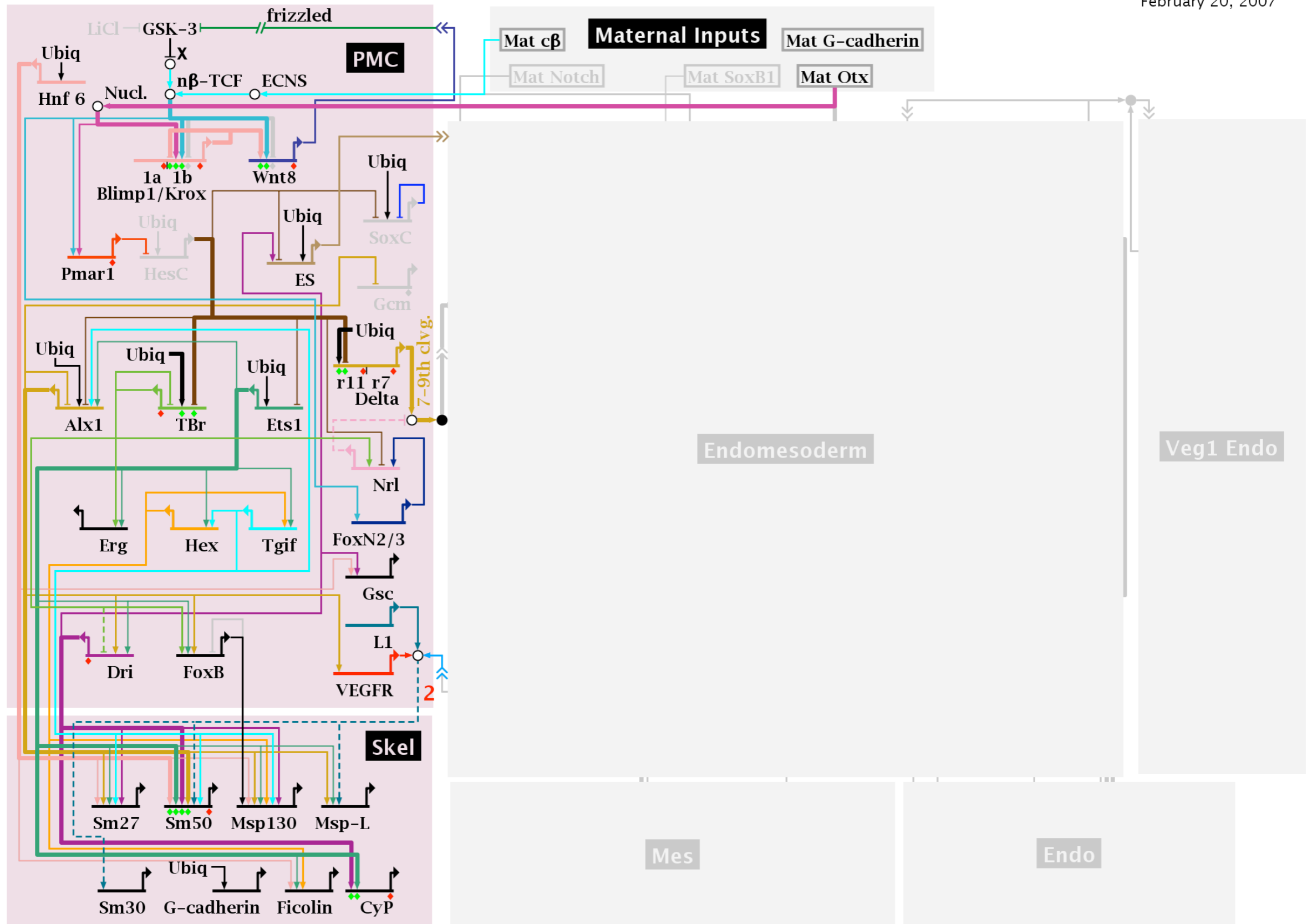


Ubiq=ubiquitous; Mat = maternal; activ = activator; rep = repressor;
 unkn = unknown; Nucl. = nuclearization; χ = β -catenin source;
 n β -TCF = nuclearized b- β -catenin-Tcf1; ES = early signal;
 ECNS = early cytoplasmic nuclearization system; Zyg. N. = zygotic Notch

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PMC 6-30 Hours

February 20, 2007

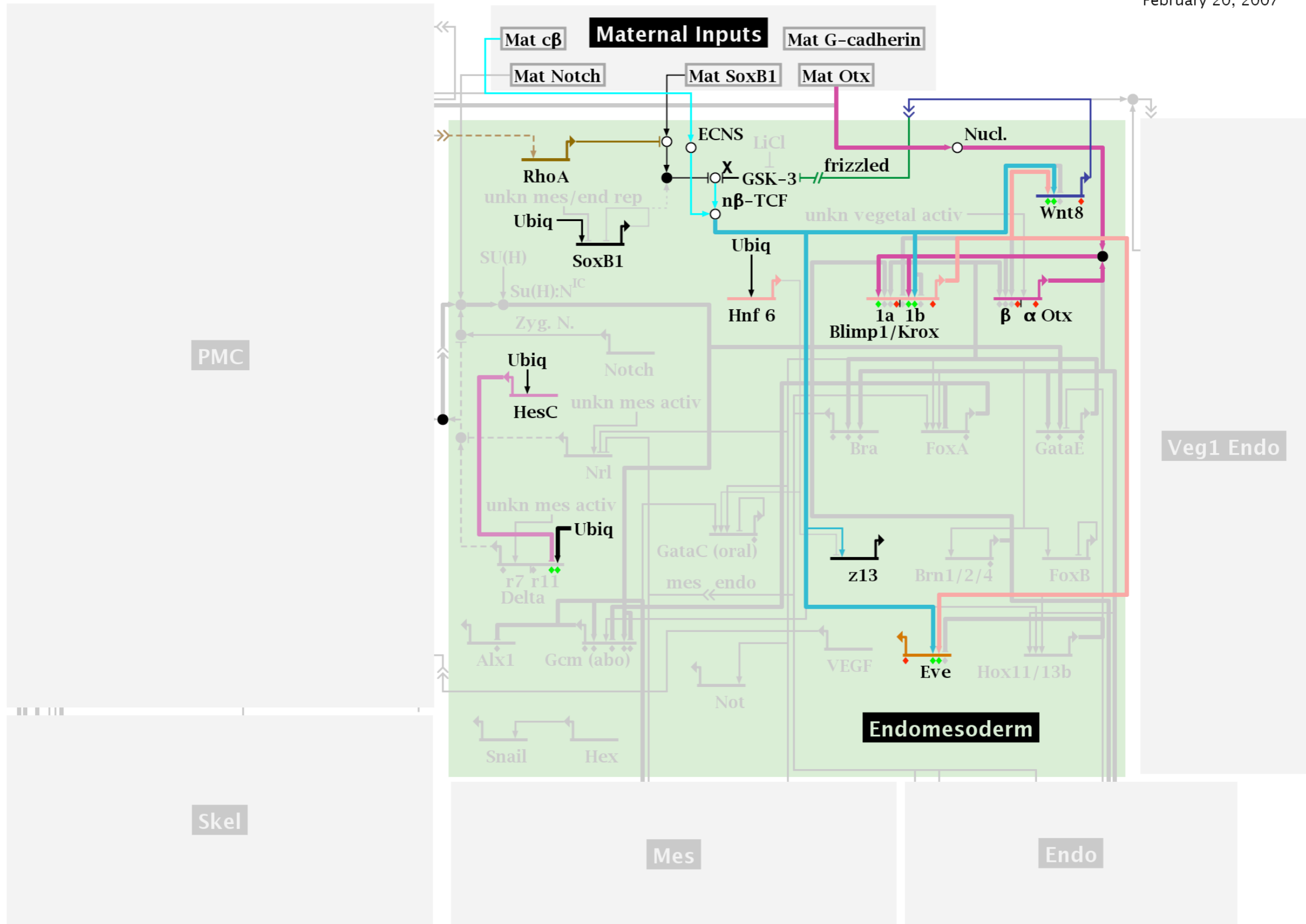


Ubiqu=ubiquitous; Mat = maternal; activ = activator; rep = repressor;
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 n β -TCF = nuclearized b- β -catenin-Tcf1; ES = early signal;
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Endomesoderm 6-11 Hours

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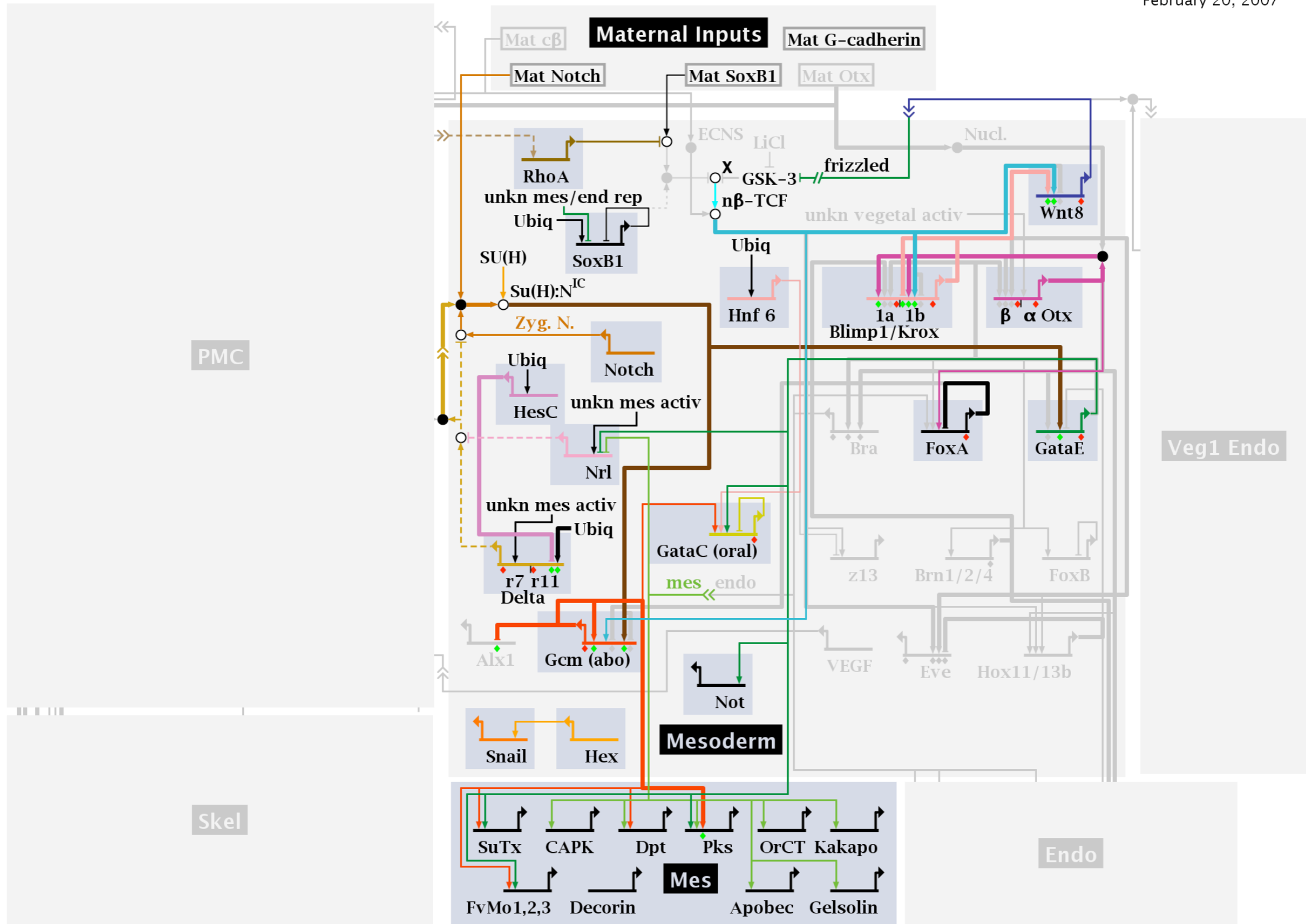


Ubiq=ubiquitous; Mat = maternal; activ = activator; rep = repressor;
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Mesoderm 12-30 Hours

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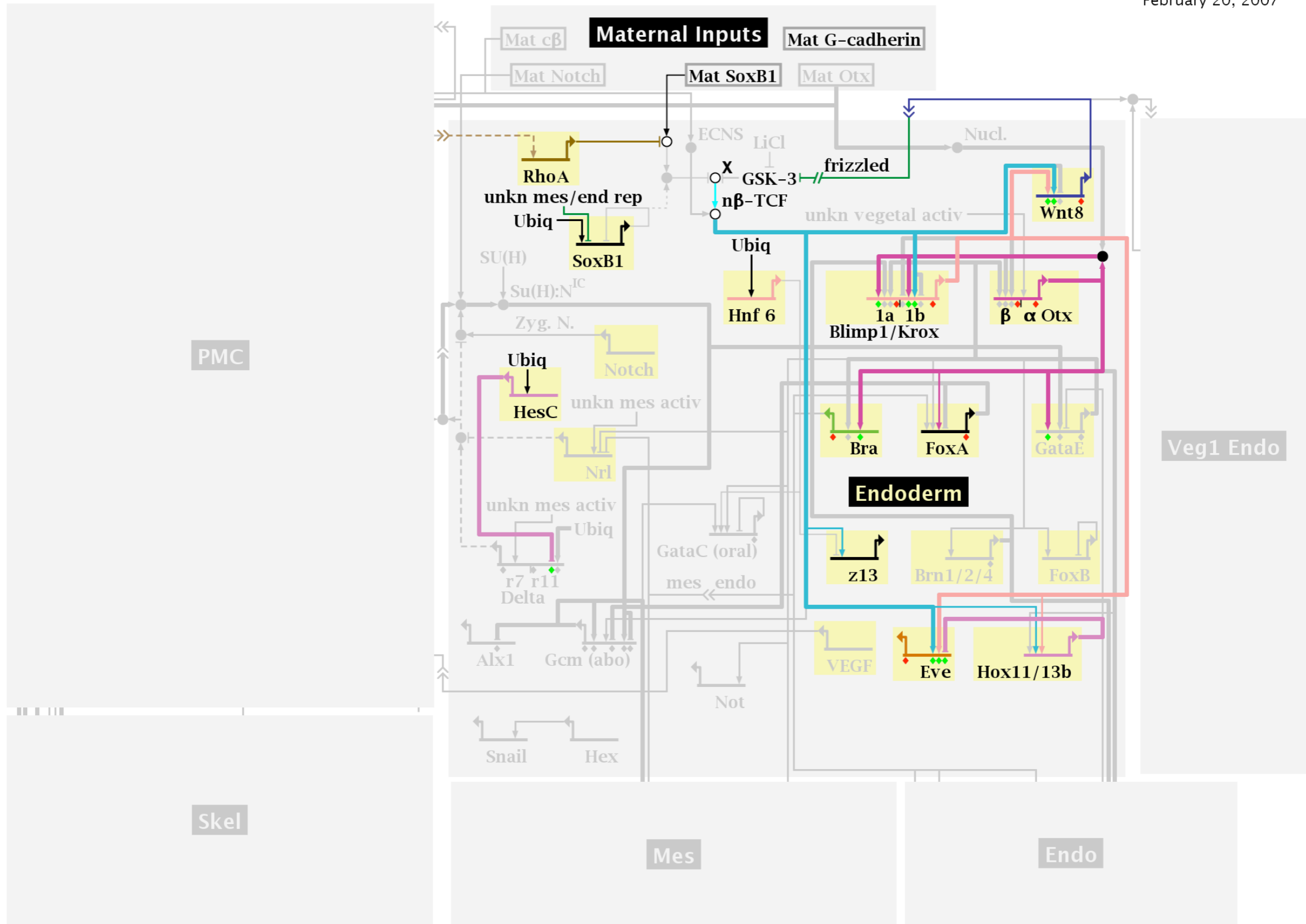


Ubiq=ubiquitous; Mat = maternal; activ = activator; rep = repressor;
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Early Endoderm 12-17 Hours

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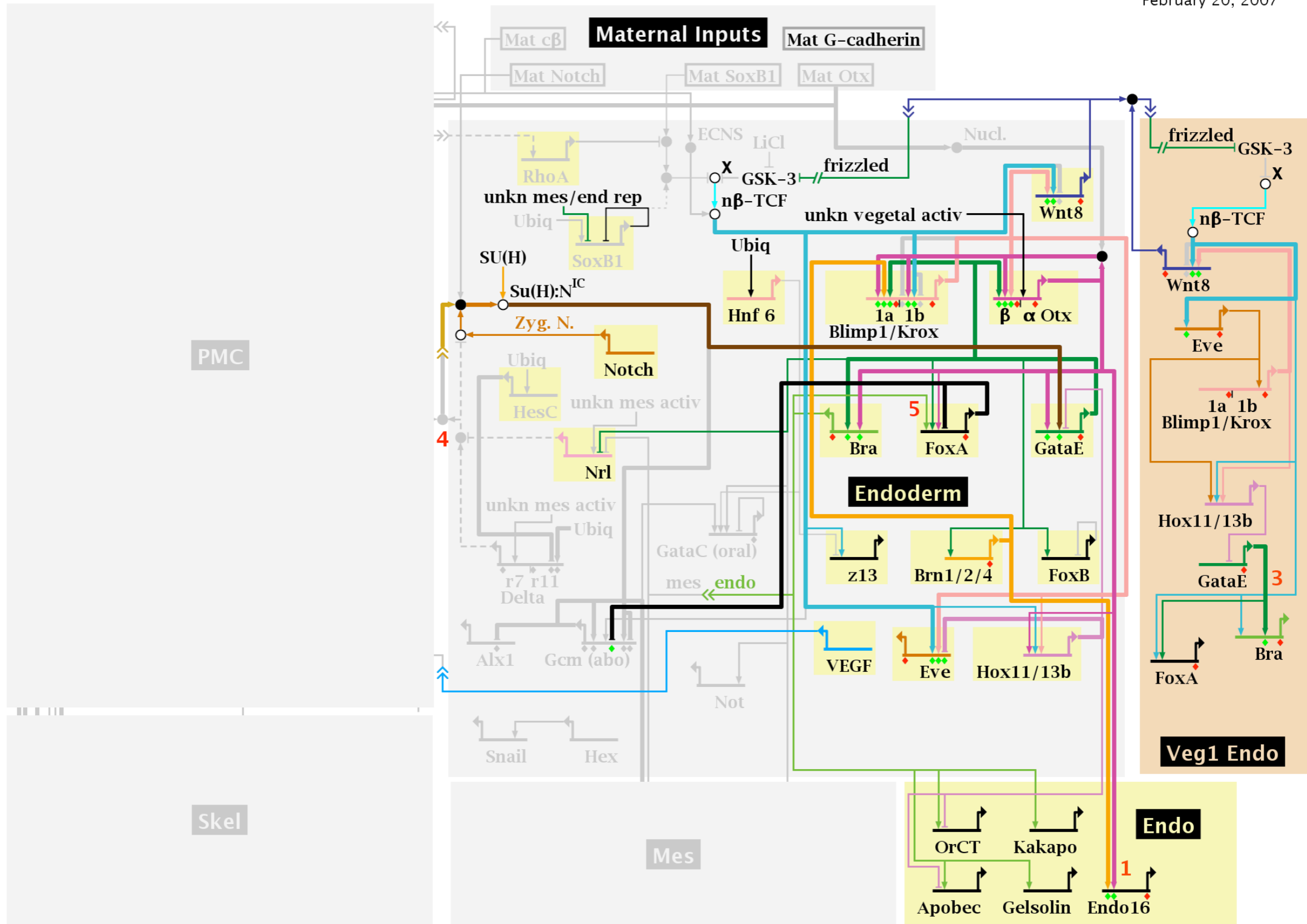


Ubiq=ubiquitous; Mat = maternal; activ = activator; rep = repressor;
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 ECNS = early cytoplasmic nuclearization system; Zyg. N. = zygotic Notch

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Endoderm with Veg1 18-30 Hours

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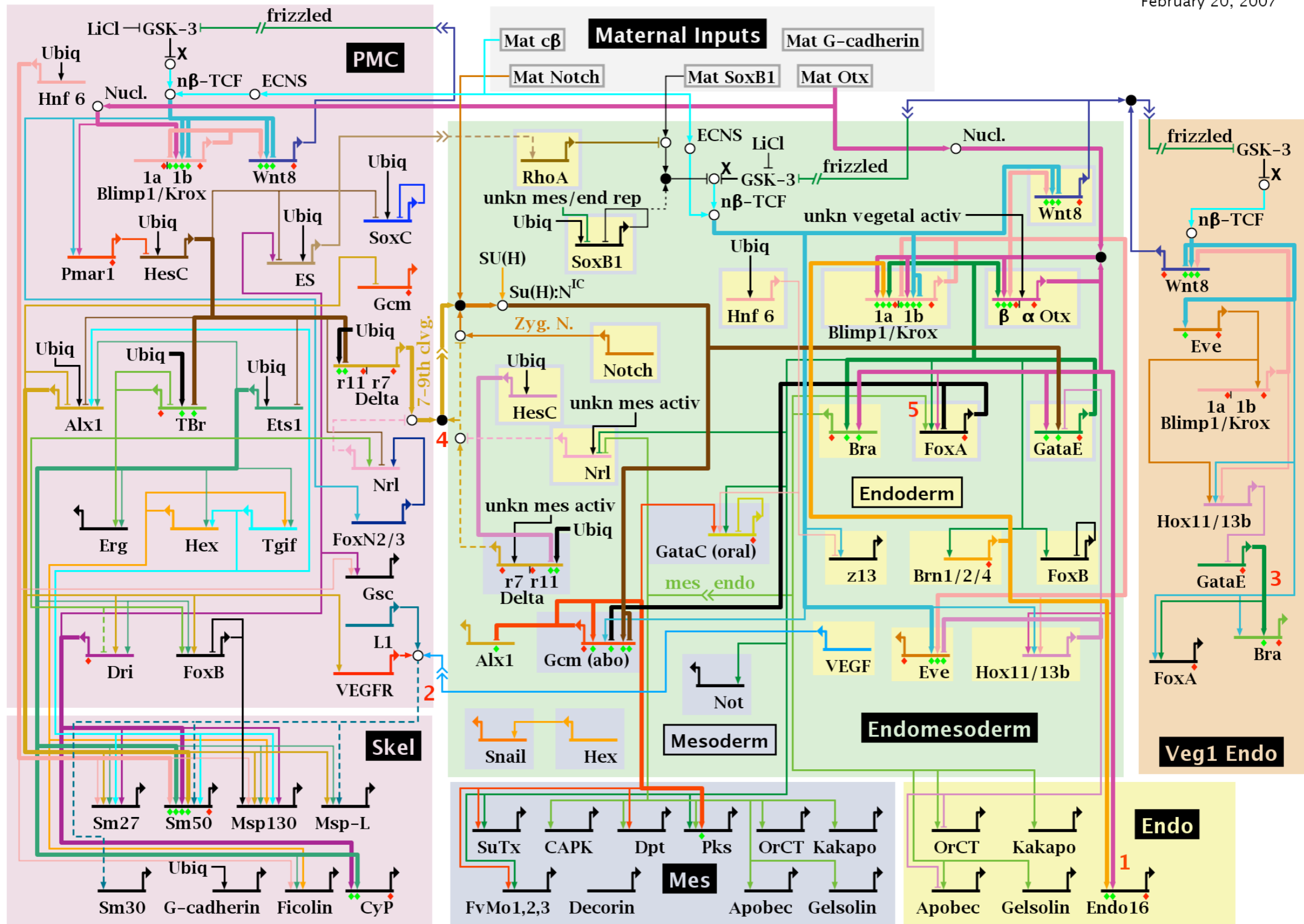


Ubiq=ubiquitous; Mat = maternal; activ = activator; rep = repressor;
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Endomesoderm Specification to 30 Hours

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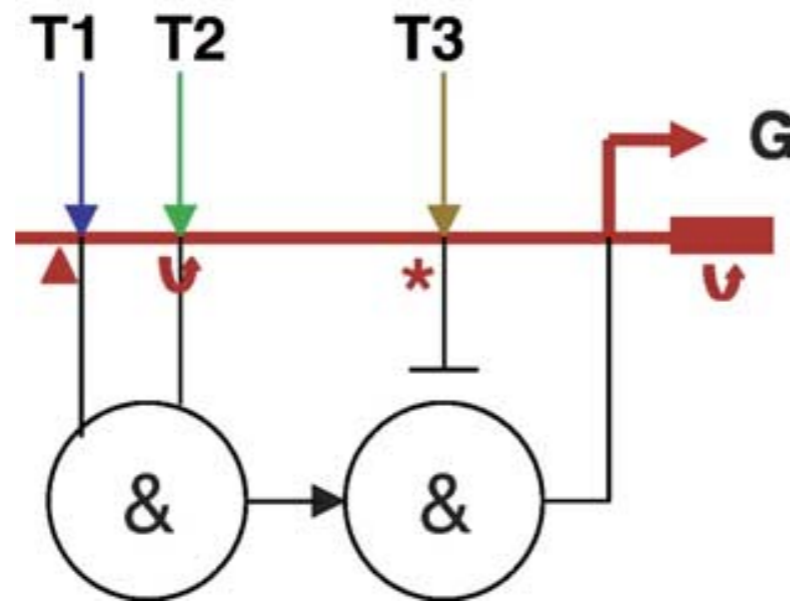


Fig. 4. Proposed DNA-based computational representation of a gene. The red horizontal line represents DNA. The portion to the left of the bent red arrow represents upstream (5') sequence. The red box to the right of the bent red arrow represents a DNA feature, such as the first exon. T1–3 are transcription factors, which in this example bind the upstream sequence and transcriptionally regulate the expression of *G*. The regulatory interactions of the three transcription factors are represented symbolically by the two circles labeled with the logical AND symbol. The bar at the end of the line from T3 to the right hand circle indicates T3 activity acts as a repressor. Since the other input to this interaction is the logical AND of T1 and T2, the output of the second interaction (and hence gene *G*) can be seen to be ((T1 AND T2) AND NOT(T3)); that is, transcription of *G* is active if T1 and T2 are both active, repressed if T3 is active, and basal otherwise. The symbols just below the line representing DNA are icons for hyperlinks to genome browsers showing detailed sequence annotations such as exons (right-hand curved arrow) known transcription factor binding sites (*) and results from DNA search algorithms (triangle).