Biochemical Reactions and Logic Computation

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(Introduction to EDA, 2013)

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Biochemical Reactions and Biology

- Complex behaviors of a living organism originate from systems of biochemical reactions
- Engineering biochemical reactions may sharpen our understanding on how nature design living organisms (in contrast to how human design electronic systems)

Outline

- Compiling program control flows into biochemical reactions
- Beyond logic computation

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- Compiling program control flows into biochemical reactions
  - Joint work with Chi-Yun Cheng, De-An Huang, Ruei-Yang Huang [ICCAD 2012]
- Beyond logic computation

Computational Biochemistry

- In living organisms, biochemical reactions carry out some form of "computations" which result in complex behaviors
- Biochemical reactions may be exploited for computation by combining a proper set of biochemical reactions
- Computation with biochemical reactions has potential applications in synthetic biology
  - In synthetic biology, known biochemical parts (DNA, mRNA, proteins, etc.) are assembled either naturally or artificially to realize desired functions

Previous Work

- Synthesizing molecular reactions has been pursued, e.g.,
  - Arithmetic operations
    - Fett *et al.* (2007, 2008)
  - Digital signal processing
    - Jiang *et al.* (2010)
  - Writing and compiling code into biochemistry
    - Shea *et al.* (2010), Senum *et al.* (2011)

Previous Work

- Still lack systematic methodology to construct complex program **control flows**
- Heavily rely on modularized reactions
- Assume reactions are of small quantities
  - Work under stochastic simulation but not ODE simulation

Our Focus

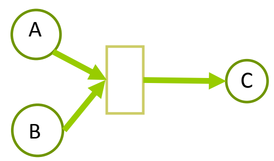
- Robustness
  - Improved reaction regulation
  - Enhanced fault tolerance
  - Valid under both stochastic and ODE simulations
- Optimality
  - Reduced number of reactions
  - Not limited to modularized reactions
- Systematic compilation methodology

Model of Computation

- Computation with biochemical reactions
  - Computation in terms of molecular quantities
  - Quantity changing rules are defined by reactions
- Example

$$A + B \rightarrow C$$

$$[C] = \min\{[A],[B]\}$$



Petri net representation

Reaction Model

- Classical chemical kinetic (CCK) model
  - ODE based simulation
    - (Empirical study shows our construction works for discrete stochastic simulation as well)
- Example:

$$\alpha A + \beta B \xrightarrow{k} \gamma C$$

$$-\frac{1}{\alpha}\frac{d[A]}{dt} = -\frac{1}{\beta}\frac{d[B]}{dt} = \frac{1}{\gamma}\frac{d[C]}{dt} = k[A]^{\alpha}[B]^{\beta}$$

Boolean & Quantitative Abstraction

- Data represented by molecular concentrations
- Control signals in terms of Boolean abstraction

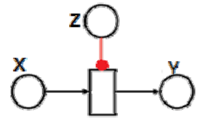
$$A_\theta = f_\theta(A) = \begin{cases} 1, & \text{if } [A] \geq \theta \\ 0, & \text{otherwise} \end{cases}$$

Reaction Execution Precedence

- In information processing, computation must be performed in a proper order
- Data dependencies must be maintained to ensure operational correctness

Precondition

- For reaction $X + Z \rightarrow Y + Z$
- Z_θ is the *precondition* $\Rightarrow$ $X \xrightarrow{Z_\theta} Y$

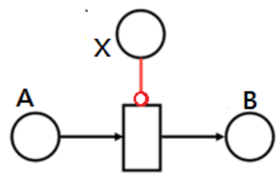


$$X \xrightarrow{A_\theta \wedge B_\theta} Y \Rightarrow X + A + B \rightarrow Y + A + B$$

$$X \xrightarrow{A_\theta \vee B_\theta} Y \Rightarrow \begin{array}{l} X + A \rightarrow Y + A \\ X + B \rightarrow Y + B \end{array}$$

Precondition

- For $X + Z \rightarrow Y + Z$,
  - At the end of the reaction, X exhausts and *Y* has the same amount as *X* before the reaction
  - We use $\neg X_\theta \wedge Y_\theta$ to denote the postcondition of the reaction
    - To represent the absence of *X*, let there be presence of some molecule, called **absence indicator**.



Absence Indicator

- Prior method [Senum and Riedel 2011]

$$\emptyset \xrightarrow{r_s} A'$$
$$A + A' \xrightarrow{r_f} A$$

Reaction rate $r_f >> r_s$

At equilibrium (when *A* is present),

$$[A'] = \frac{r_s}{r_f}[A]$$

- The amount of *A*' is sensitive to the amount of *A*
  - This "leakage" degrades the robustness
  - Can only be applied to stochastic model

Absence Indicator

- Dimerized absence indicator

$$\emptyset \xrightarrow{r_s} A'$$
$$A + A' \xrightarrow{r_f} A$$
$$2A' \underset{r_f}{\overset{r_s}{\rightleftharpoons}} A^*$$

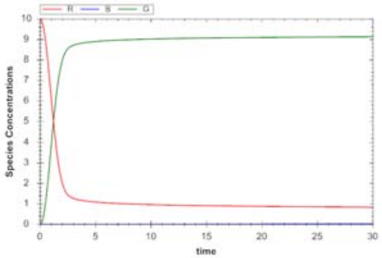
At equilibrium (when *A* is present),

$$[A^*] = \frac{r_s}{r_f}[A']^2$$

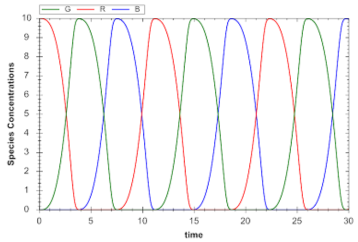
- *A** is further suppressed by the presence of *A'*
- *A** remains little even if there is a leakage of *A*

Absence Indicator

$$R \xrightarrow{\neg B_\theta} G$$
$$G \xrightarrow{\neg R_\theta} B$$
$$B \xrightarrow{\neg G_\theta} R$$



prior absence indicator



dimerized absence indicator

(by ODE simulation with SBW simulator)

Reaction Buffer

- Reaction series:

(1) $A \rightarrow B$, $B \xrightarrow{\neg A_\theta} A$

After execution for some time, A exceeds reaction threshold; precondition is violated.

(2) $A \rightarrow B$, $B \xrightarrow{\neg A_\theta} C$, $C \xrightarrow{\neg B_\theta} A$

The "buffer" reaction avoids the leakage problem

Compilation Strategy

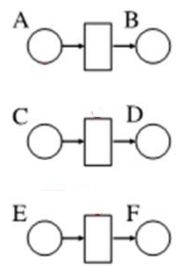
1. Identify **Linear**, **Looping**, **Branching** statements and create corresponding control flow reactions.
2. Resolve violation of *preconditions* or *postconditions*, and introduce buffer if necessary.
3. Decompose reactions for practical realization
4. Optimize

Linear Flow

- Without regulation, reactions are concurrent

Main Reactions

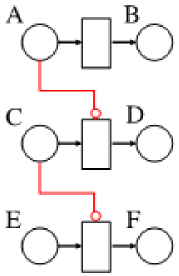
01	$A \rightarrow B$
02	$C \rightarrow D$
03	$E \rightarrow F$



Linear Flow

- When reactions are intended to be in a sequential manner, precondition can be imposed as follows:

	Main Reactions	Preconditions
01	$A \rightarrow B$	
02	$C \rightarrow D$	$\neg A_\theta$
03	$E \rightarrow F$	$\neg C_\theta$



Branching Statements

	Main Reactions	Preconditions
	...	
01	$Q \rightarrow R$	
02	**if** $P_1(A,B)$	$\neg Q_\theta$
03	$S_1 \rightarrow T_1$	$Post(P_1)$
	...	
04	$S_i \rightarrow T_i$	
05	$H \rightarrow I$	$\neg S_{i\theta}$
06	**else if** $P_2(A,B)$	$\neg Q_\theta$
07	$U_1 \rightarrow V_1$	$Post(P_2)$
	...	
08	$U_j \rightarrow V_j$	
09	$H \rightarrow I$	$\neg U_{j\theta}$
10	**else**	$\neg Q_\theta$
11	$W_1 \rightarrow X_1$	$Post(\neg P_1 \wedge \neg P_2)$
	...	
12	$W_k \rightarrow X_k$	
13	$H \rightarrow I$	$\neg W_{k\theta}$
14	$Y \rightarrow Z$	$\neg H_\theta$
	...	

Branching Statements

	Main Reactions	Preconditions
	...	
01	$Q \rightarrow R$	
02	**if** $P_1(A,B)$	$\neg Q_\theta$
03	$S_1 \rightarrow T_1$	$Post(P_1)$
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	...	
12	$W_k \rightarrow X_k$	
13	$H \rightarrow I$	$\neg W_{k\theta}$
14	$Y \rightarrow Z$	$\neg H_\theta$
	...	

Same precondition to start if-else judgment

Branching Statements

	Main Reactions	Preconditions
	...	
01	$Q \rightarrow R$	
02	**if** $P_1(A,B)$	$\neg Q_\theta$
03	$S_1 \rightarrow T_1$	$Post(P_1)$
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11	$W_1 \rightarrow X_1$	$Post(\neg P_1 \wedge \neg P_2)$
	...	
12	$W_k \rightarrow X_k$	
13	$H \rightarrow I$	$\neg W_{k\theta}$
14	$Y \rightarrow Z$	$\neg H_\theta$
	...	

Design judgment carefully.
Use mutually exclusive postconditions to enter different code block.

Branching Statements

Main Reactions	Preconditions
…	
$Q \rightarrow R$	
if $P_1(A,B)$	$\neg Q_\theta$
$S_1 \rightarrow T_1$	$Post(P_1)$
…	
$S_i \rightarrow T_i$	
$H \rightarrow I$	$\neg S_{i\theta}$
else if $P_2(A,B)$	$\neg Q_\theta$
$U_1 \rightarrow V_1$	$Post(P_2)$
…	
$U_j \rightarrow V_j$	
$H \rightarrow I$	$\neg U_{j\theta}$
else	$\neg Q_\theta$
$W_1 \rightarrow X_1$	$Post(\neg P_1 \wedge \neg P_2)$
…	
$W_k \rightarrow X_k$	
$H \rightarrow I$	$\neg W_{k\theta}$
$Y \rightarrow Z$	$\neg H_\theta$
…	

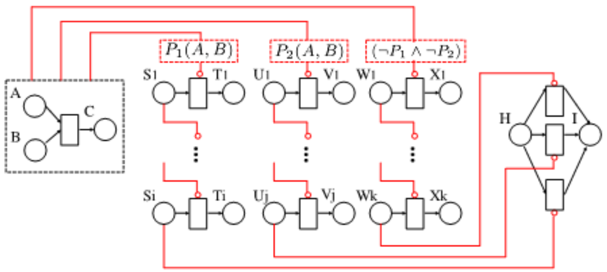
Different reaction leads to the same ending reaction

Branching Statements

Main Reactions	Preconditions
…	
$Q \rightarrow R$	
if $P_1(A,B)$	$\neg Q_\theta$
$S_1 \rightarrow T_1$	$Post(P_1)$
…	
$S_i \rightarrow T_i$	
$H \rightarrow I$	$\neg S_{i\theta}$
else if $P_2(A,B)$	$\neg Q_\theta$
$U_1 \rightarrow V_1$	$Post(P_2)$
…	
$U_j \rightarrow V_j$	
$H \rightarrow I$	$\neg U_{j\theta}$
else	$\neg Q_\theta$
$W_1 \rightarrow X_1$	$Post(\neg P_1 \wedge \neg P_2)$
…	
$W_k \rightarrow X_k$	
$H \rightarrow I$	$\neg W_{k\theta}$
$Y \rightarrow Z$	$\neg H_\theta$
…	

Same ending reaction to leave branching for each program block.

Branching Statements



Petri net visualization of branching statements:
Using $A+B \rightarrow C$ to judge (A>B)?

Looping Statement

Main Reactions	Preconditions
$Q \rightarrow R$	
while $P(A,B)$	$\neg Q_\theta \cdot \neg F_\theta$
$\ldots \rightarrow F$	$Post(P)$
…	
$F \rightarrow \ldots$	
$X \rightarrow Y$	$Post(\neg P)$

Looping Statement

Main Reactions	Preconditions
$Q \rightarrow R$	
while $P(A, B)$	$\neg Q_\theta \cdot \neg F_\theta$
$\ldots \rightarrow F$	$Post(P)$
$\cdots$	
$F \rightarrow \ldots$	
$X \rightarrow Y$	$Post(\neg P)$

Judgment is made when
(1)Previous reaction finished
(2)End of every single loop

Looping Statement

Main Reactions	Preconditions
$Q \rightarrow R$	
while $P(A, B)$	$\neg Q_\theta \cdot \neg F_\theta$
$\ldots \rightarrow F$	$Post(P)$
$\cdots$	
$F \rightarrow \ldots$	
$X \rightarrow Y$	$Post(\neg P)$

Use judgment result as pre ition
to determine whether er
or not.

Loop body

Looping Statement

Main Reactions	Preconditions
$Q \rightarrow R$	
while $P(A, B)$	$\neg Q_\theta \cdot \neg F_\theta$
$\ldots \rightarrow F$	$Post(P)$
$\cdots$	
$F \rightarrow \ldots$	
$X \rightarrow Y$	$Post(\neg P)$

Executed when Looping condition not satisfied

Loop body

Case Study: Division

```
Division(A, B)
  begin
    while A ≥ B
      A := A − B
      Q := Q + 1
    R := A
  end
```

Case Study: Division

Main Reactions		Preconditions
01	**while** $[A] \geq [B]$	
02	$(A + B \rightarrow D)$	$\neg G_\theta$
03	$C \rightarrow Q + E$	$A_\theta \wedge \neg B_\theta$
04	$D \rightarrow F$	$\neg C_\theta$
05	$E \rightarrow G$	$\neg D_\theta$
06	$F \rightarrow B$	$\neg E_\theta$
07	$G \rightarrow C$	$\neg F_\theta$
08	$D \rightarrow R$	$\neg A_\theta$

C of unit amount initially

Case Study: Division

Main Reactions		Preconditions
01	**while** $[A] \geq [B]$	
02	$(A + B \rightarrow D)$	$\neg G_\theta$
03	$C \rightarrow Q + E$	$A_\theta \wedge \neg B_\theta$
04	$D \rightarrow F$	$\neg C_\theta$
05	$E \rightarrow G$	$\neg D_\theta$
06	$F \rightarrow B$	$\neg E_\theta$
07	$G \rightarrow C$	$\neg F_\theta$
08	$D \rightarrow R$	$\neg A_\theta$

A:=A-B

Q:=Q+1

Case Study: Division

Main Reactions		Preconditions
01	**while** $[A] \geq [B]$	
02	$(A + B \rightarrow D)$	$\neg G_\theta$
03	$C \rightarrow Q + E$	$A_\theta \wedge \neg B_\theta$
04	$D \rightarrow F$	$\neg C_\theta$
05	$E \rightarrow G$	$\neg D_\theta$
06	$F \rightarrow B$	$\neg E_\theta$
07	$G \rightarrow C$	$\neg F_\theta$
08	$D \rightarrow R$	$\neg A_\theta$

$A \Leftarrow A - B$

$D \Leftarrow B$

$B \Leftarrow 0$

If $A > B$, B will exhaust and A will have amount $[A] - [B]$ remains.

Case Study: Division

Main Reactions		Preconditions
01	**while** $[A] \geq [B]$	
02	$(A + B \rightarrow D)$	$\neg G_\theta$
03	$C \rightarrow Q + E$	$A_\theta \wedge \neg B_\theta$
04	$D \rightarrow F$	$\neg C_\theta$
05	$E \rightarrow G$	$\neg D_\theta$
06	$F \rightarrow B$	$\neg E_\theta$
07	$G \rightarrow C$	$\neg F_\theta$
08	$D \rightarrow R$	$\neg A_\theta$

$Q \Leftarrow Q + C$

The amount of Q increment by C, (We set $C=1$).

Case Study: Division

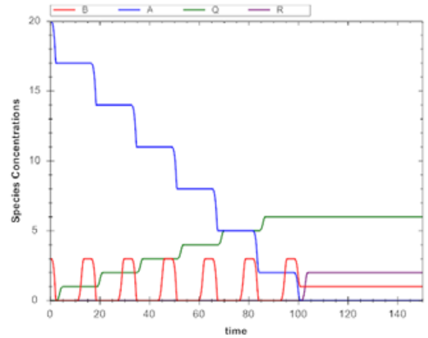
Main Reactions	Preconditions
while $[A] \geq [B]$	
$(A + B \rightarrow D)$	$\neg G_\theta$
$C \rightarrow Q + E$	$A_\theta \wedge \neg B_\theta$
$D \rightarrow F$	$\neg C_\theta$
$E \rightarrow G$	$\neg D_\theta$
$F \rightarrow B$	$\neg E_\theta$
$G \rightarrow C$	$\neg F_\theta$
$D \rightarrow R$	$\neg A_\theta$

$B \Leftarrow D$

B must regain value before next judgment

Case Study: Division

- Division 20÷3



(ODE simulation with SBW)

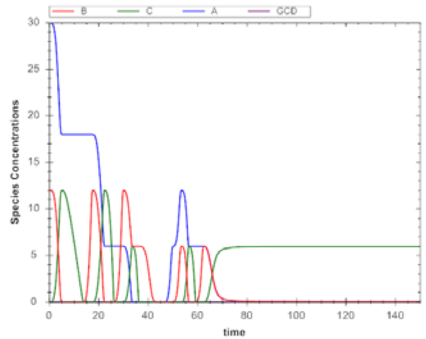
Case Study: GCD

```
begin
    while A ≠ B
        if A > B
            A := A − B
        else if B > A
            swap(A, B)
    GCD := A
end
```

may cause a serious problem because $[A]$ almost never exactly equal $[B]$
1000 != 1001

Case Study: GCD

- *GCD(30,12)*



(ODE simulation with SBW)

Failure due to imperfect condition A ≠ B

Case Study: GCD

```
GreatestCommonDivisor_err_toler(A, B, Z)
  begin
      while |A − B| > Z
         if A > B + Z
            A := A − B
         else if B > A + Z
            swap(A, B)
      GCD := A
  end
```

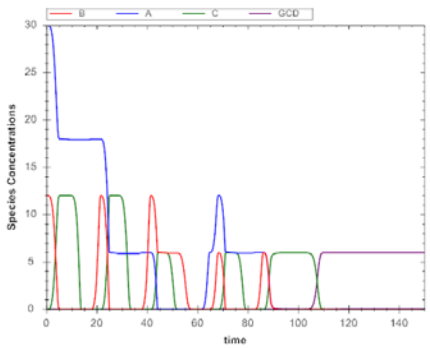
Z is a necessarily small constant , indicating the error tolerant range.

Case Study: GCD

	Main Reactions	Preconditions	
01	**while** $\|[A]-[B]\| > [Z]$		
02	$(A + B \to C)$	$\neg H_\theta \wedge \neg F_\theta$	
03	$(A + Z \to X)$	$\neg H_\theta \wedge \neg F_\theta \wedge \neg B_\theta$	
04	$(B + Z \to Y)$	$\neg H_\theta \wedge \neg F_\theta \wedge \neg A_\theta$	
05	**if** $[A] > [B] + [Z]$		
06	$C \to D$	$A_\theta \wedge \neg B_\theta \wedge \neg Z_\theta$	$A = A - B$
07	$X \to A + Z$	$\neg C_\theta \wedge \neg B_\theta$	
08	$D \to H$	$\neg C_\theta$	
09	$H \to B$	$\neg D_\theta$	
10	**else if** $[B] > [A] + [Z]$		
11	$C \to E$	$\neg A_\theta \wedge B_\theta \wedge \neg Z_\theta$	
12	$B \to G$	$\neg C_\theta \wedge \neg A_\theta$	
13	$Y \to B + Z$	$\neg C_\theta \wedge \neg A_\theta$	$swap(A, B)$
14	$E \to F$	$\neg B_\theta$	
15	$G \to A$	$\neg E_\theta$	
16	$F \to A + B$	$\neg G_\theta$	
17	$C \to GCD$	$\neg A_\theta \wedge \neg B_\theta$	

Case Study: GCD

- *GCD(30,12)*



(ODE simulation with SBW)

Correct answer obtained by enhanced error tolerance

Future work

- Biological realization of the compilation approach
- Minimization of molecular species
- From discrete/static to continuous/dynamic computation?
  - Feedbacks
  - Robustness issues

Outline

- Compiling program control flows into biochemical reactions
- Beyond logic computation

Beyond Logic Computation

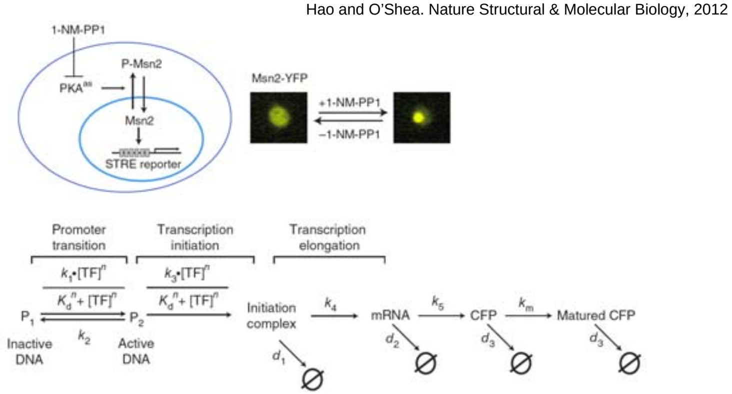
- A signal processing perspective
  - Modulators, filters, and signal processing
- A control perspective
  - Sensors, actuators (motors), and decision making

Signal Processing Perspective

- Transcription factor translocation example

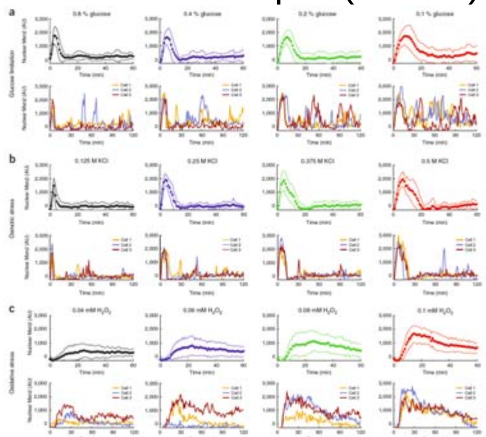
Nuclear translocation of *S. cerevisiae* stress response TF Msn2

Hao and O'Shea. Nature Structural & Molecular Biology, 2012



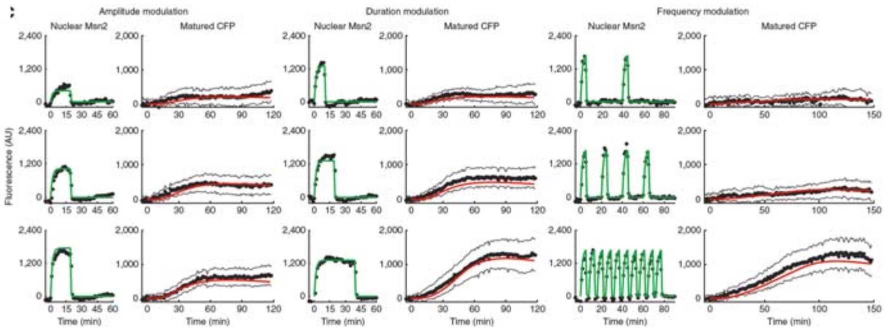
Signal Processing Perspective

- TF translocation example (cont'd)



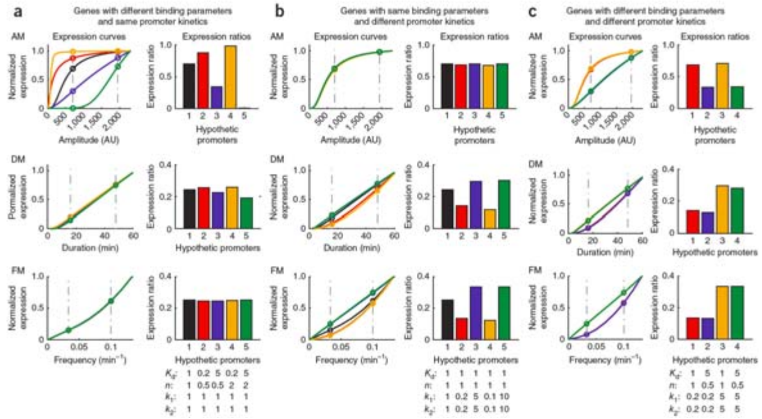
Signal Processing Perspective

TF translocation example (cont'd)



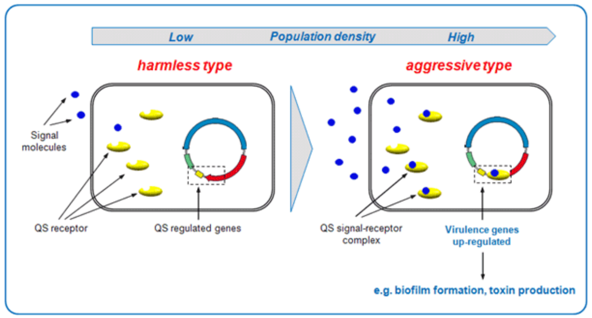
Signal Processing Perspective

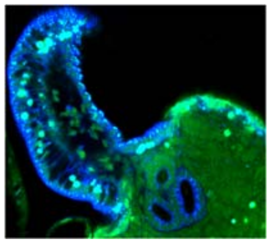
TF translocation example (cont'd)



Control Perspective

Quorum sensing example

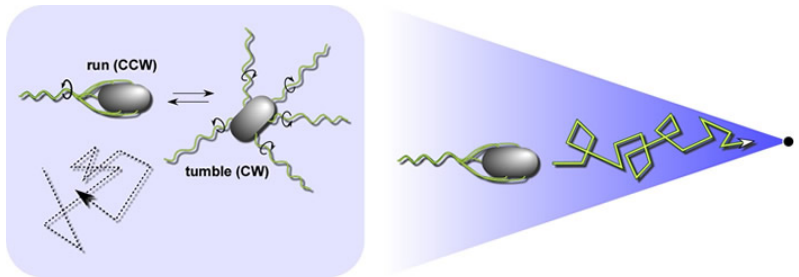




Symbiotic association between the squid Euprymna scolopes and the luminous bacterium Vibrio fischeri

Control Perspective

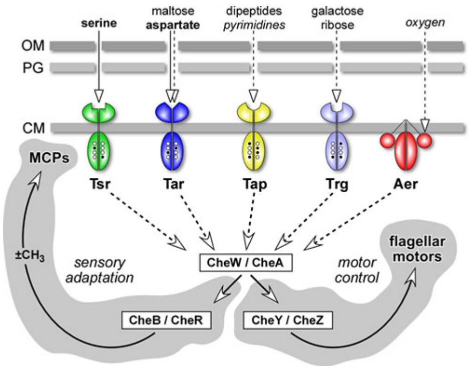
Chemotaxis example

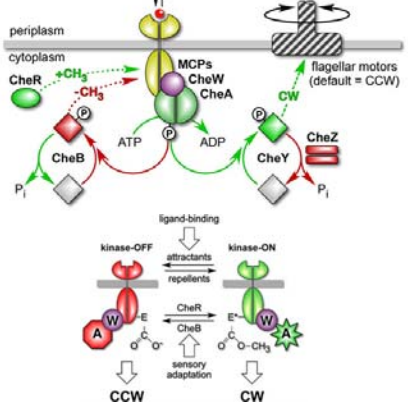


http://chemotaxis.biology.utah.edu/Parkinson_Lab/projects/ecolichemotaxis/ecolichemotaxis.html

Control Perspective

- Chemotaxis example (cont'd)





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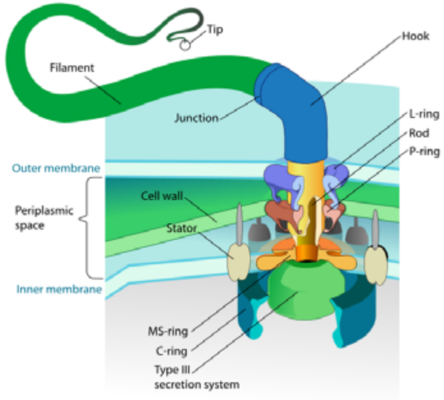
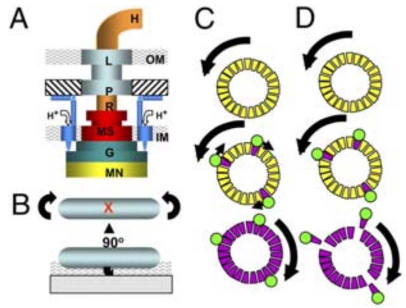
Control Perspective

- Chemotaxis example (cont'd)





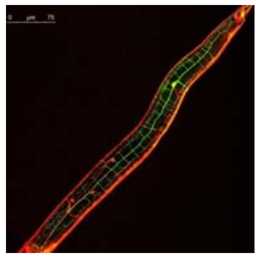
Manson M D PNAS 2010;107:11151-11152

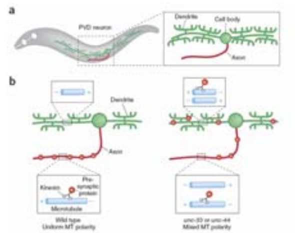
Beyond Systems Biology

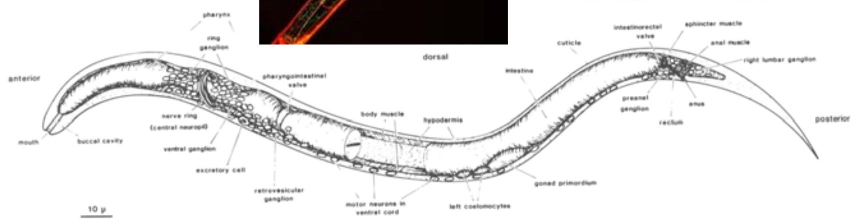
- Systems biology share strong similarities with systems neuroscience, although fundamental mechanisms are quite different
  - In biology, biochemical reactions are the fundamental mechanism
  - In neuroscience, electrical communications are the fundamental mechanism

Connection to Neuroscience

- C. elegans nervous system

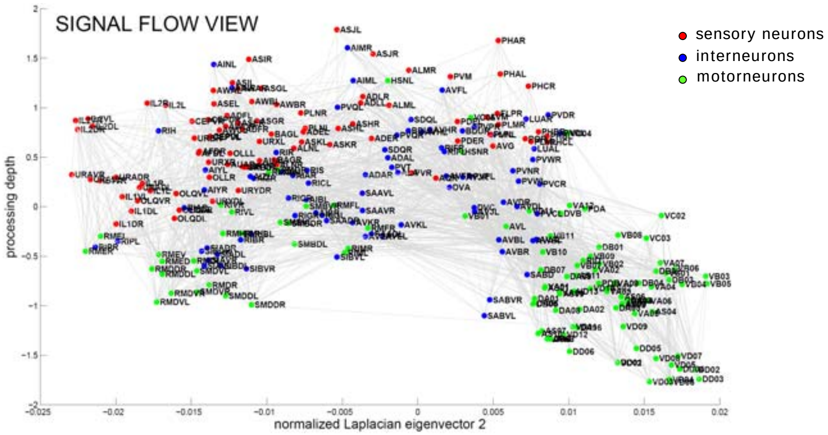






Connection to Neuroscience

- Connectome of C. elegans (302) neurons



Connection to Neuroscience

- C. elegans neuron circuitry

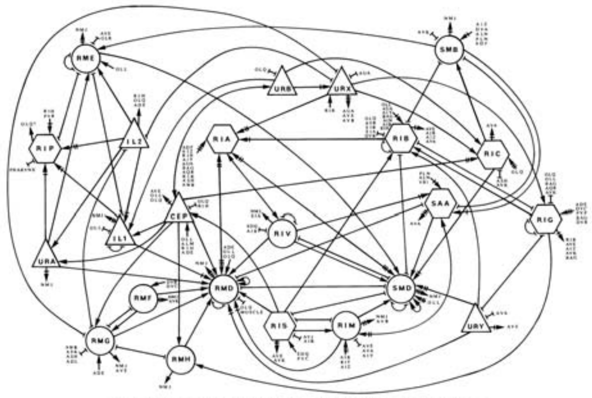


FIGURE 21. (c) Circuitry associated with the motoneurons in the nerve ring.

Summary

- Program control flows can be systematically compiled into biochemical reactions
- Discrete computation, though convenient abstraction for genetic circuits, is not a universal approach to systems and synthetic biology
- New computation models needed to decipher various open questions in systems biology and systems neuroscience