HW3

Sunday, September 29, 2024 2:17 PM

1. **Fixed points**. Consider the following 10-variable model of the *lac* operon, from class, where the 3 parameters are added with "frozen" update functions.

$$
\begin{aligned}
f_M &= \overline{R} \wedge \overline{R_m} \wedge C & f_{A_m} &= L \vee L_m \\
f_B &= M & f_L &= \overline{G_e} \wedge P \wedge L_e \\
f_P &= M & f_{L_m} &= \overline{G_e} \wedge ((L_{em} \wedge P) \vee L_e) \\
f_C &= \overline{G_e} & f_{L_e} &= L_e \\
f_R &= \overline{A} \wedge \overline{A_m} & f_{L_{em}} &= L_{em} \\
f_{R_m} &= (\overline{A} \wedge \overline{A_m}) \vee R & f_{G_e} &= G_e \\
f_A &= L \wedge B
\end{aligned}
$$

Use Macaulay2 to compute a Gröbner basis of the ideal $I = (f_{x_1} + x_1, \ldots, f_{x_{13}} + x_{13})$, in the quotient ring $\mathbb{F}_2[x_1, \ldots, x_{13}]/(x_i^2 - x_i)$. Solve the resulting system by hand to find all fixed points of the original Boolean model. Code is provided on the course website.

```
-- Define a ring of polynomials in 9 variables

R = ZZ/2[x1,x2,x3,x4,x5,x6,x7,x8,x9,x10,Le,Lem,Ge];

-- Shortcut for AND and OR functions

RingElement | RingElement :=(x,y)->x+y+x*y;
RingElement & RingElement :=(x,y)->x*y;

-- Define a quotient ring, where each x_i^2 = x_i

J = ideal(x1^2-x1, x2^2-x2, x3^2-x3, x4^2-x4, x5^2-x5, x6^2-x6, x7^2-x7, x8^2-x8, x9^2-x9, x10^2-x10, Le^2-Le, Lem^2-Lem, Ge^2-Ge);
Q = R / J;

-- This is the 10-variable lac operon model, with parameters taken to be variables

f1 = (1+x5) & (1+x6) & x4;
f2 = x1;
f3 = x1;
f4 = 1+Ge;
f5 = (1+x7) & (1+x8);
f6 = ((1+x7) & (1+x8)) | x5;
f7 = x2 & x9;
f8 = x9 | x10;
f9 = (1+Ge) & x3 & Le;
f10 = (1+Ge) & ((Lem & x3) | Le);
fLe = Le;
fLem = Lem;
fGe = Ge;
```

LOAD SAVE

tutorials/default.m2

```
-- Compute the ideal to find the fixed point(s)

I = ideal(f1+x1, f2+x2, f3+x3, f4+x4, f5+x5, f6+x6, f7+x7, f8+x8, f9+x9, f10+x10, fLe+Le, fLem+Lem, fGe+Ge)

-- Compute a Groebner basis

G = gens gb I
```

```
i1 : -- Define a ring of polynomials in 9 variables
     R = ZZ/2[x1,x2,x3,x4,x5,x6,x7,x8,x9,x10,Le,Lem,Ge];
i2 :
     -- Shortcut for AND and OR functions
     RingElement | RingElement :=(x,y)->x+y+x*y;
i3 : RingElement & RingElement :=(x,y)->x*y;
i4 :
     -- Define a quotient ring, where each x_i^2 = x_i
     J = ideal(x1^2-x1, x2^2-x2, x3^2-x3, x4^2-x4, x5^2-x5, x6^2-x6, x7^2-x7, x8^2-x8, x9^2-x9, x10^2-x10, Le^2-Le, Lem^2-Lem, Ge^2-Ge);
o4 : Ideal of R
i5 : Q = R / J;
i6 :
     -- This is the 10-variable lac operon model, with parameters taken to be variables
     f1 = (1+x5) & (1+x6) & x4;
i7 : f2 = x1;
i8 : f3 = x1;
i9 : f4 = 1+Ge;
i10 : f5 = (1+x7) & (1+x8);
i11 : f6 = ((1+x7) & (1+x8)) | x5;
i12 : f7 = x2 & x9;
i13 : f8 = x9 | x10;
i14 : f9 = (1+Ge) & x3 & Le;
i15 : f10 = (1+Ge) & ((Lem & x3) | Le);
i16 : fLe = Le;
i17 : fLem = Lem;
i18 : fGe = Ge;
i19 :
      -- Compute the ideal to find the fixed point(s)
      I = ideal(f1+x1, f2+x2, f3+x3, f4+x4, f5+x5, f6+x6, f7+x7, f8+x8, f9+x9, f10+x10, fLe+Le, fLem+Lem, fGe+Ge)
```

o19 = ideal$(x4\,x5\,x6 + x4\,x5 + x4\,x6 + x1 + x4,\ x1 + x2,\ x1 + x3,\ x4 + Ge + 1,\ x7\,x8 + x5 + x7 + x8 + 1,\ x5\,x7\,x8 + x5\,x7 + x5\,x8 + x7\,x8 + x6 + x7 + x8 + 1,\ x2\,x9 + x7,\ x9\,x10 + x8 + x9 + x10,\ x3\,Le$ $Ge + x3\,Le + x9,\ x3\,Le\,Lem\,Ge + x3\,Le\,Lem + x3\,Lem\,Ge + x3\,Lem + Le\,Ge + x10 + Le, 0, 0, 0)$

o19 : Ideal of Q

```
i20 :
      -- Compute a Groebner basis
      G = gens gb I
```

o20 = $(\ x8 + x10 \quad x7 + x9 \quad x6 + x10 + 1 \quad x5 + x10 + 1 \quad x4 + Ge + 1 \quad x3 + x10 \quad x2 + x10 \quad x1 + x10 \quad Le\,Ge + x9 + Le \quad x10\,Ge \quad x9\,Ge \quad x9\,Lem + x10\,Lem + x9 + x10 \quad x10\,Le + x9 \quad x9\,Le + x9$ $\quad x9\,x10 + x9\ )$

o20 : Matrix $Q^1 \longleftarrow Q^{15}$

$X_8 = X_{10} = \overline{X_6} = \overline{X_5} = X_3 = X_2 = X_1$

$X_7 = X_9$

$X_9 \wedge \overline{Lem} = X_{10} \wedge \overline{Lem}$

$\wedge \overline{Ge} = X_9$

$x_7 = x_9$

$\overline{x_4} = G_e$

$L_e \wedge \overline{G_e} = x_9$

$L_e(G_e+1) = x_9$

$L_eG_e + x_9 + L_e = 0$

$x_{10}G_e = 0 \qquad x_{10} \wedge G_e = 0$

$x_9G_e = 0 \qquad x_9 \wedge G_e = 0$

$\Rightarrow G_e = 1 \Rightarrow x_{10}, x_9 = 0$

$G_e = 0 \Rightarrow x_9, x_{10} = 1$ or 0

$x_9 \wedge \overline{L_{em}} = x_{10} \wedge \overline{L_{em}}$

$x_9(L_{em}+1) = x_{10}(L_{em}+1)$

$L_{em} = 0 = x_9 \Rightarrow x_{10} = 0$

$x_9L_{em} + x_{10}L_{em} + x_9 + x_{10} = 0$

$x_{10}L_e + x_9 = 0 \Rightarrow x_{10} \wedge L_e = x_9$

$x_9L_e + x_9 = 0 \Rightarrow x_9(L_e+1) = 0$ — $L_e = 1 \Rightarrow x_9 = 1$ or 0; $L_e = 0 \Rightarrow x_9 = 0$

$x_9x_{10} + x_9 = 0 \Rightarrow x_9(x_{10}+1) = 0$ — $x_9 = 1 \Rightarrow x_{10} = 1$; $x_9 = 0 \Rightarrow x_{10} = 1$ or 0

$A(B+1) = 0$

$A = 1 \Rightarrow B = 1$

$A = 0 \Rightarrow B = 0$ or 1

I promise I did this by hand

$G_e = 1$ $\qquad\qquad$ $G_e = 0$

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \\ x_7 \\ x_8 \\ x_9 \\ x_{10} \\ L_e \\ L_{em} \\ G_e \end{bmatrix} \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \end{bmatrix} \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \end{bmatrix} \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 0 \end{bmatrix} \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{bmatrix} \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}$$

other solutions don't make sense ($L_{em} = 1$ $L_e = 0$)

2. **Bistability**. Consider the following model of the tryptophanase (*tna*) operon in E. coli:

$$\begin{aligned} f_A &= M \wedge \overline{\gamma} & f_P &= \overline{W} \wedge \overline{W_m} \\ f_B &= M & f_W &= \omega_e \wedge B \\ f_C &= \overline{\gamma} & f_{W_m} &= (\omega_{em} \wedge B) \vee \omega_e \vee W \\ f_M &= C \wedge \overline{P} \end{aligned}$$

There are three parameters: γ is glucose, ω_e is high levels of extracellular tryptophan, and ω_{em} represents (at least) medium levels of extracellular tryptophan.

(a) Let γ, ω_e, and ω_{em} be "frozen" variables, making this a 10-variable model. Use Cyclone to find the attractors. Code is provided on the course website.

```
NUMBER OF VARIABLES: 10
NUMBER OF STATES: 2

x1 = x4 * (1+Ge)
x2 = x4
x3 = 1+Ge
x4 = x3 * (1+x5)
x5 = (1+x6) * (1+x7)
x6 = we * x2
x7 = (wem * x2) | we | x6
we = we
wem = wem
Ge = Ge
```

```
Number of cycles (components): 13

COMPONENT #1:
  component size: 128
  fixed point: [0 0 1 0 1 0 0 0 0 0]

COMPONENT #2:
  component size: 128
  fixed point: [0 0 0 0 1 0 0 0 0 1]

COMPONENT #3:
  component size: 6
  fixed point: [0 0 1 0 1 0 0 0 1 0]

COMPONENT #4:
  component size: 128
  fixed point: [0 0 0 0 1 0 0 0 1 1]

COMPONENT #5:
  component size: 128
  fixed point: [1 1 1 1 0 1 1 1 0 0]
```

```
COMPONENT #6:
  component size: 128
  fixed point: [0 0 0 0 0 0 1 1 0 1]

COMPONENT #7:
  component size: 128
  fixed point: [1 1 1 1 0 1 1 1 1 0]

COMPONENT #8:
  component size: 128
  fixed point: [0 0 0 0 0 0 1 1 1 1]

COMPONENT #9:
  component size: 20
  cycle of length 4:
    [0 0 1 0 0 0 0 0 1 0] ->
    [0 0 1 1 1 0 0 0 1 0] ->
    [1 1 1 0 1 0 0 0 1 0] ->
    [0 0 1 0 1 0 1 0 1 0] ->
    [0 0 1 0 0 0 0 0 1 0]
```

```
COMPONENT #10:
  component size: 40
  cycle of length 4:
    [0 0 1 0 0 0 1 0 1 0] ->
    [0 0 1 1 0 0 0 0 1 0] ->
    [1 1 1 1 1 0 0 0 1 0] ->
    [1 1 1 0 1 0 1 0 1 0] ->
    [0 0 1 0 0 0 1 0 1 0]

COMPONENT #11:
  component size: 8
  cycle of length 2:
    [1 1 1 0 0 0 0 0 1 0] ->
    [0 0 1 1 1 0 1 0 1 0] ->
    [1 1 1 0 0 0 0 0 1 0]
```

```
COMPONENT #12:
  component size: 44
  cycle of length 4:
    [1 1 1 0 0 0 1 0 1 0] ->
    [0 0 1 1 0 0 1 0 1 0] ->
    [1 1 1 1 0 0 0 0 1 0] ->
    [1 1 1 1 1 0 1 0 1 0] ->
    [1 1 1 0 0 0 1 0 1 0]

COMPONENT #13:
  component size: 10
  fixed point: [1 1 1 1 0 0 1 0 1 0]
```

(b) Fix $(\gamma, \omega_e, \omega_{em}) = (0, 0, 1)$ as constants to get a 7-variable model, which assumes no glucose and medium levels of extracellular tryptophan. Use BoolNet to find the attactors under an asynchronous update, and summarize your findings. This can be done with the command

```
> getAttractors(tnaModel,type="asynchronous",startStates=256)
```

How does this compare to the synchronous state space?

```
Attractor 1 is a simple attractor consisting of 1 state(s):

 |--<------|
 V         |
 1111001   |
 V         |
 |-->------|


Genes are encoded in the following order: A B C M P W WM

Attractor 2 is a simple attractor consisting of 1 state(s):

 |--<------|
 V         |
 0010100   |
 V         |
 |-->------|
```

There are 6 components when updated synchronously and only 2 when updated asynchronously that match $\gamma = 0$ $w_e = 0$ $w_{em} = 1$

(c) Explain how/why this model exhibits bistability.

After looking at the attractors the difference is in W_m. Looking at f_{W_m} since $W_e = 0 \Rightarrow W = 0$ you get two possibilities. The first is a feedback if there already is W_{em} or secondly a feedback if there is no W_{em} already