Mathematical Modeling for the (Mathematically) Faint of Heart

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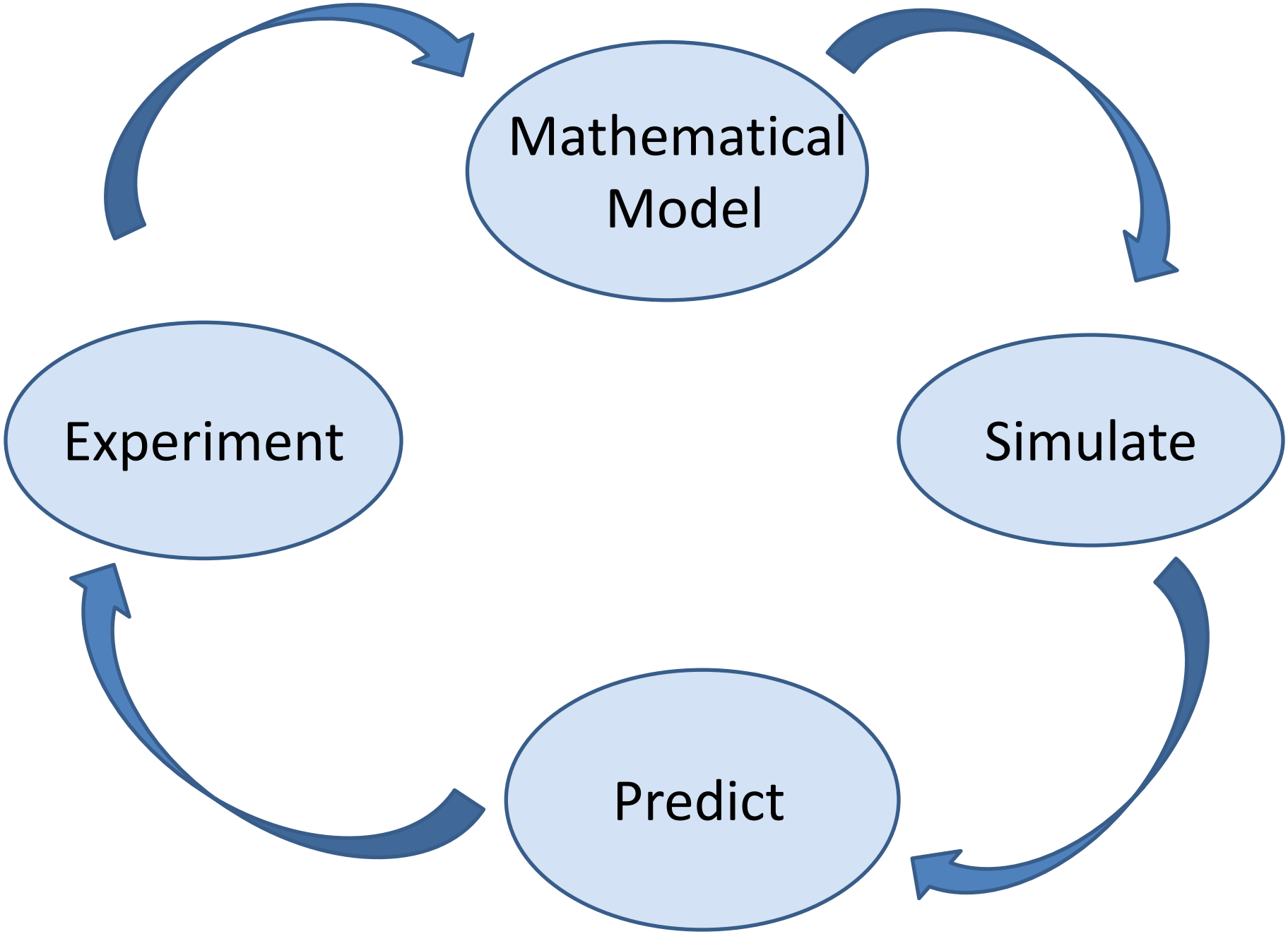
- How can we develop effective drugs for the treatment of rheumatoid arthritis?
- If we understood the cell cycle, could we understand the mechanisms of cancer?
- How does a microbe lead to the production of greenhouse gases?


Mathematical Model
Simulate
Predict
Experiment

Standard approach to building a mathematical model of a biological system

Identify actors/agents:

e.g., genes, cells, populations

Describe reactions and interactions:

Genes are up- or down-regulated; cells take up or secrete iron; populations increase or decrease

Next step…

Describe the interactions mathematically.

Traditionally, this involves systems of ODEs or PDEs.

BUT….

$$\frac{ds}{dt} = k_{-1}c - k_1 se \qquad \frac{de}{dt} = (k_{-1} + k_2)c - k_{-1} se$$

$$\frac{dc}{dt} = k_1 se - (k_{-1} + k_2)c \qquad \frac{dp}{dt} = k_2 c$$

Another approach…

Describe how the system changes discretely using a transition table instead of continuously using a DE.

A toy example

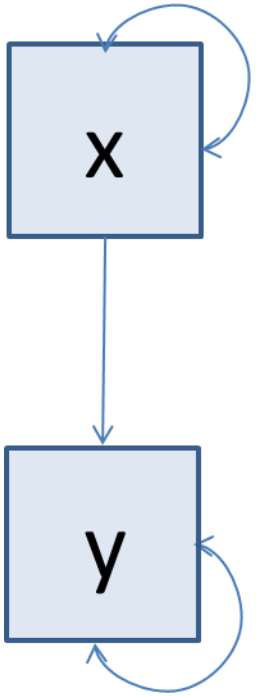
Our system has two genes, x and y, which are either on (1) or off (0).

What happens at time t +1 depends on the state of the system at time t.

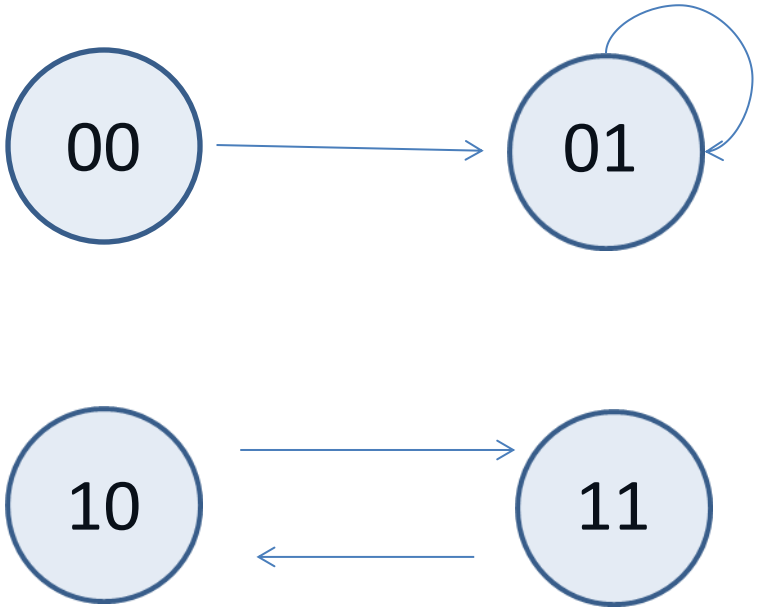
Gene x is the boring gene:
If it is off, it stays off. If it is on, it stays on.

Gene y is more interesting:
If both x and y are on, then y turns off.
If either x or y is off, then y turns on.

x(t)	y(t)	x(t+1)	y(t+1)
0	0	0	1
0	1	0	1
1	0	1	1
1	1	1	0



What happens in the long run?
One fixed point and one limit cycle



The general framework

1. Identify the agents as variables, x_1, x_2, x_3, ….
2. Each variable takes discrete values in the set

{0,1,2,…,p-1} where p is prime.

3. A state of the system is an assignment of values to the variables. Construct a table that describes how each state transitions from time t to time t+1.

4. Choose a starting point and iterate until you reach either a fixed point steady state or a limit cycle.

The problem…

1 variable → p states

2 variables → p^2 states

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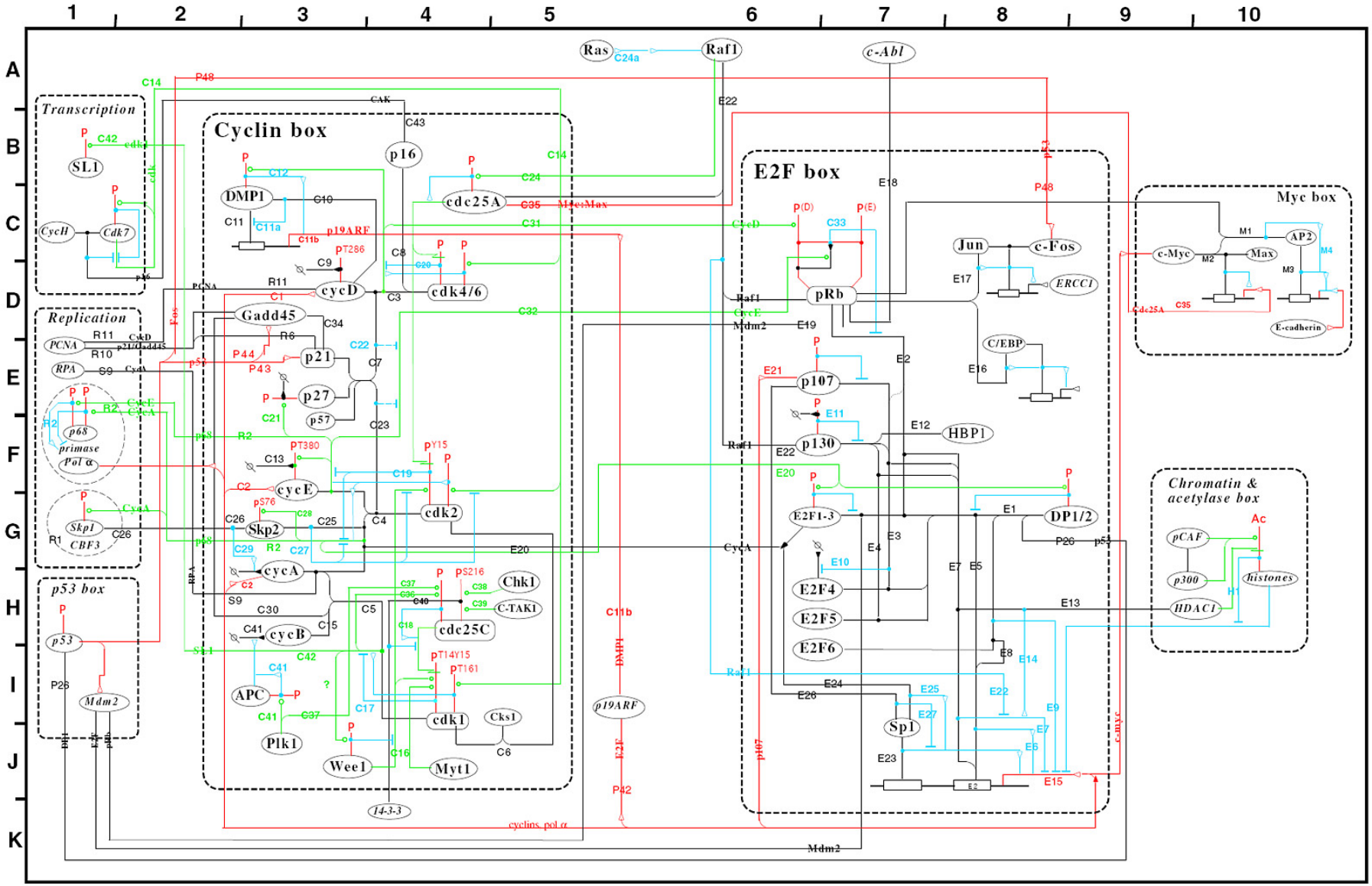
n variables → WAY TOO MANY states

The mammalian cell cycle has more than 60 variables, so more than 1.2 x 10^{18} states!



Algebra to the rescue!

1. Use LaGrange interpolation to construct polynomials $f_i(x_1,x_2,\ldots,x_n)$ over F_p which interpolate the transition table.
2. Use Gröbner basis methods to solve this system of equations to identify fixed points and limit cycles:

$$f_1^m(x_1,x_2,\ldots,x_n) = x_1$$

$$f_2^m(x_1,x_2,\ldots,x_n) = x_2$$

$$\vdots$$

$$f_n^m(x_1,x_2,\ldots,x_n) = x_n$$

A *really* short course in Gröbner bases

The theme: Reduce a hard problem to a simpler one.

Example: To solve systems of linear equations, we use Gaussian elimination to "uncouple" the variables, thus reducing the given system to one that's easier to solve.

For systems of polynomials in one variable:
Use the Euclidean algorithm to find the GCD.
Unless the polynomials are relatively prime that method will lead to a common solution.

Example: Do $x^6 - 1 = 0$ and $x^4 - 1 = 0$ have a common solution? Note

$$gcd(x^6 - 1, x^4 - 1) = x^2 - 1 .$$

We can easily solve $x^2 - 1 = 0$

For systems of polynomials in several variables (over your favorite algebriacally closed field), we use the same idea:

Gröbner basis methods tell us how to construct a simpler, but equivalent system.

Given a set of polynomials, a reduced Gröbner basis Is another set of polynomials which generate the same ideal and will,therefore, have the same common roots (if any). So it's equivalent.

The good news:
A reduced Gröbner basis will always include exactly one polynomial of one variable, which can be solved (maybe numerically). So it's simpler.

So, solve the easy equation and back substitute!

Example: Solve this system over C:

$$x^2 - yz - 3 = 0$$
$$y^2 - \mathrm{xz} - 4 = 0$$
$$z^2 - \mathrm{xy} - 5 = 0$$

A reduced Gröbner basis is

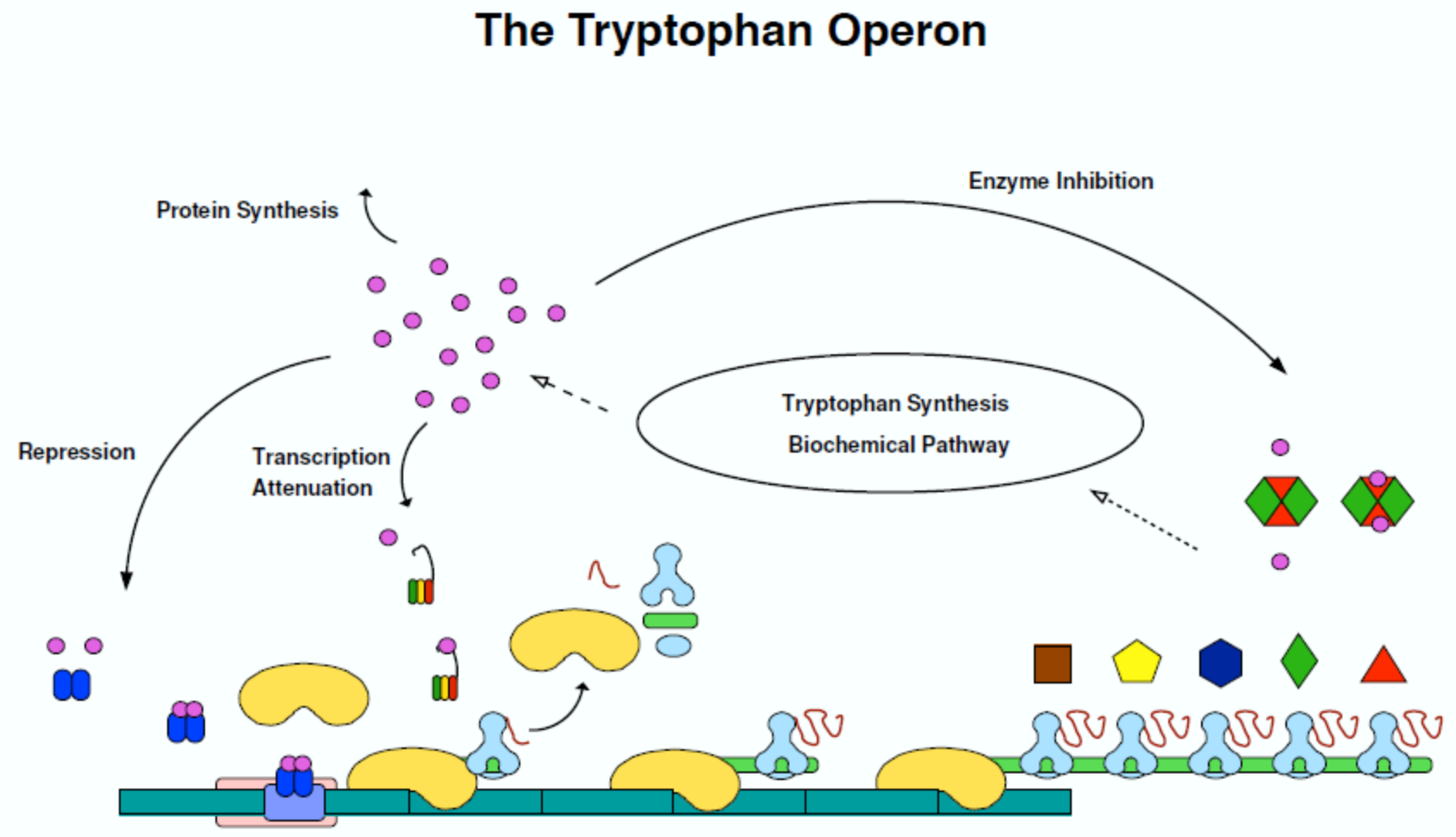
$$x + \frac{11}{13}\mathrm{z} = 0$$
$$y - \frac{1}{13}\mathrm{z} = 0$$
$$z^2 - \frac{169}{36} = 0$$

Solving the third equation gives us values for z and then we can back substitute.

Summary of discrete modeling using polynomial dynamical systems

1. Identify the agents as variables, x_1, x_2, x_3, …. where each variable takes values in F_p
2. Construct a table that describes how each state transitions from time t to time t+1.
3. Use LaGrange interpolation to construct polynomials $f_i(x_1,x_2,\ldots,x_n)$ over F_p which interpolate the transition table.
4. Use Gröbner basis methods to solve this system of equations to identify fixed points and limit cycles.

Modeling the Tryptophan operon in *E. coli*—three negative feedback loops



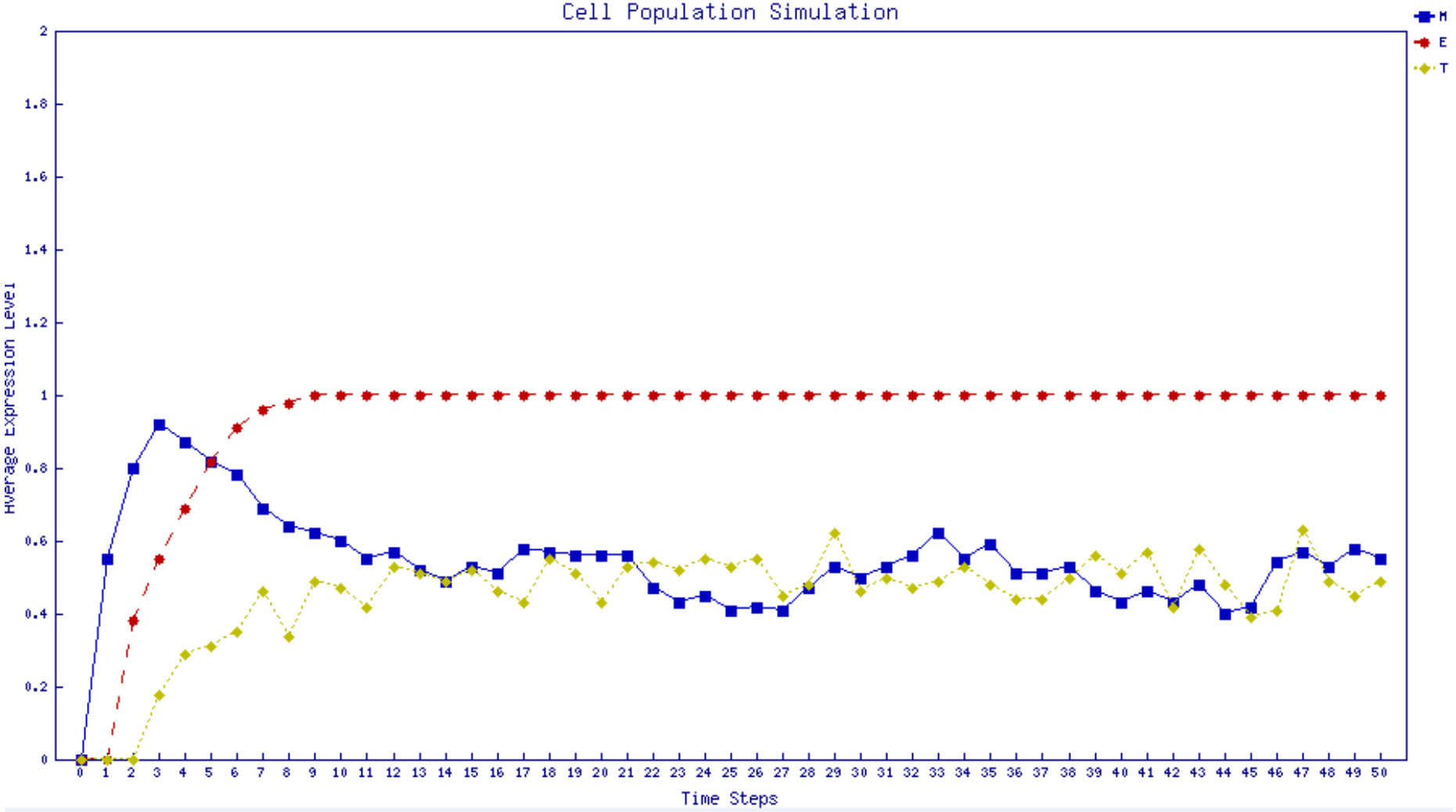
Three variables:

mRNA (M); enzyme (E); tryptophan (T)

Transition table constructed to reflect the biological properties of the system

What I expected: Fixed point steady state

What I got: Not quite that…


Cell Population Simulation
M
E
T
Average Expression Level
Time Steps
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50

Follow-up for undergraduate research

Start with my model – critique, repair, refine

---- introduce appropriate time delays

----- find estimates of propensities

----- simulate different mutants

Build a new model for a different amino acid (e.g., histidine uses only attenuation) and/or a different bacterium (e.g. *B. subtilis*)

Bottom line

Mathematical modelling has a role in solving hard problems.

There are lots of types of mathematical models. Some of them do not require differential equations, and are therefore more accessible to biologists and to a broader spectrum of mathematicians.

Commercial message!!!

Check out the MAA Prep course this summer at Sweet Briar College

Mathematical Biology: Beyond Calculus

http://www.maa.org/prep/2013/biology.html