Repressilator

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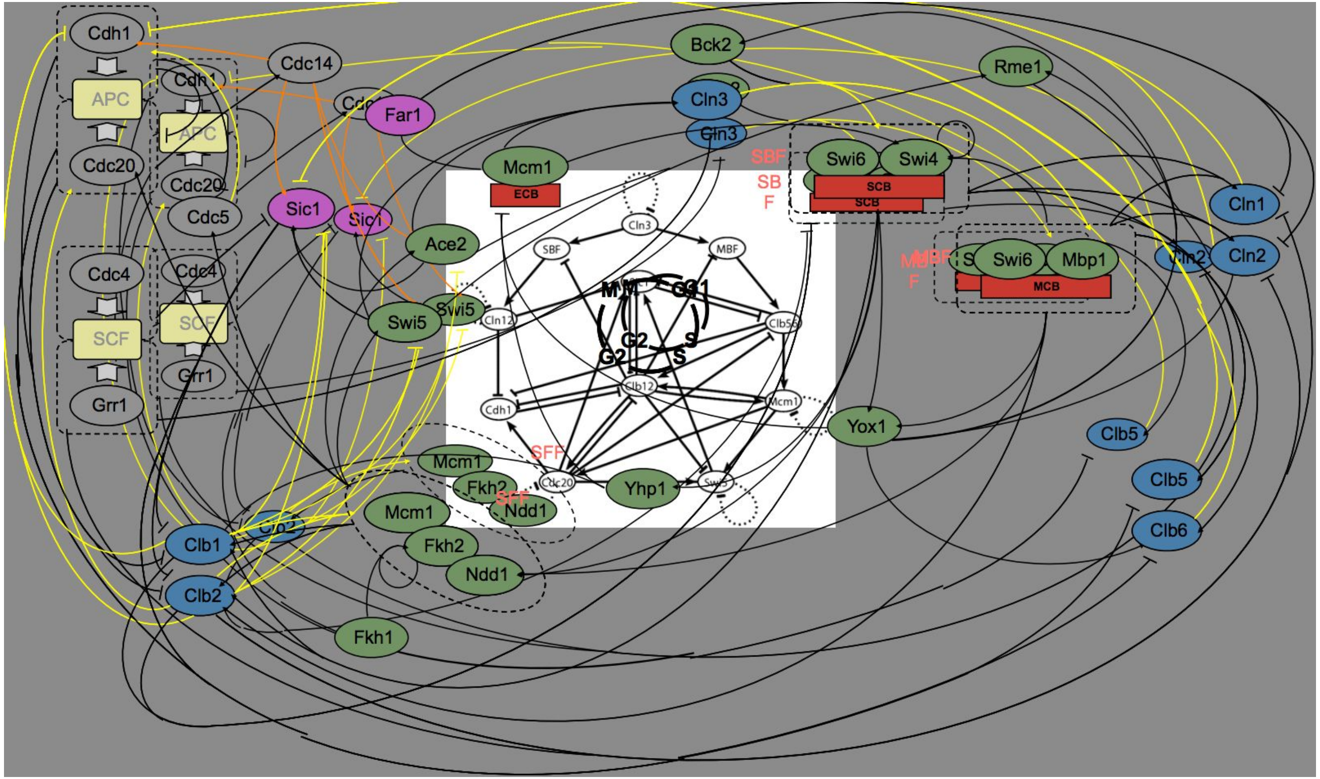
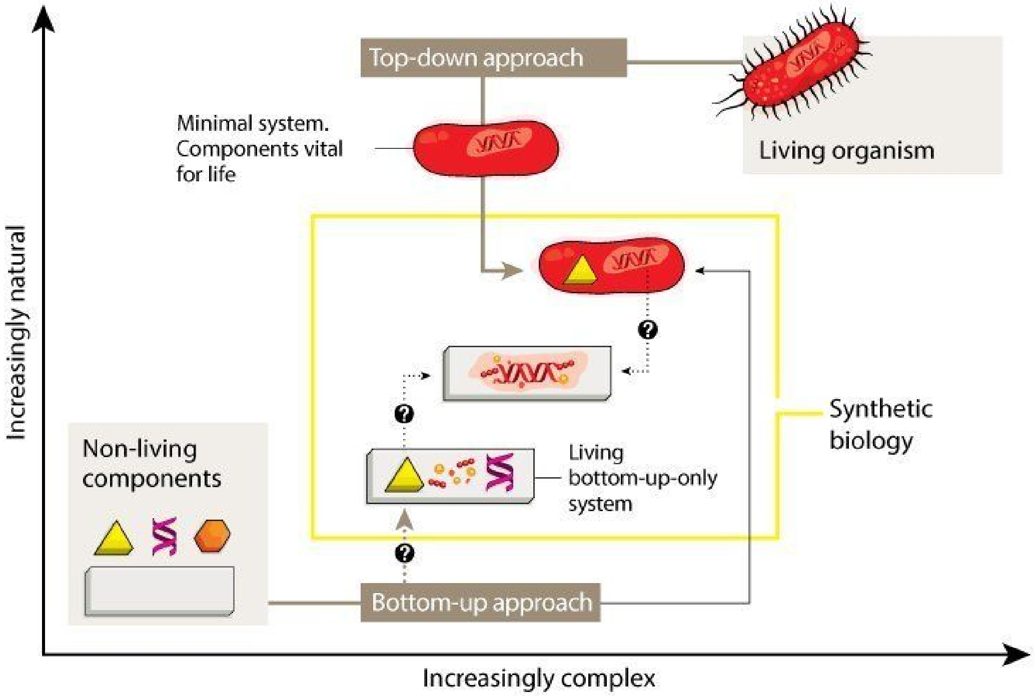
Complex Genetic Networks

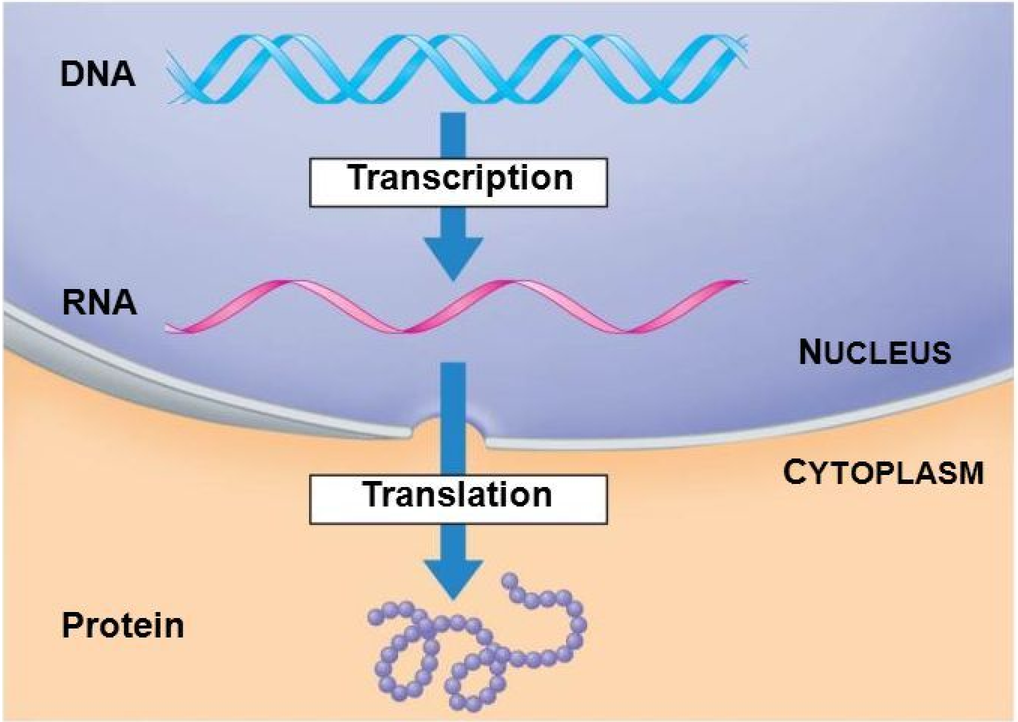


(Hasty) Welcome to BioInformatics 284. Slide 20.

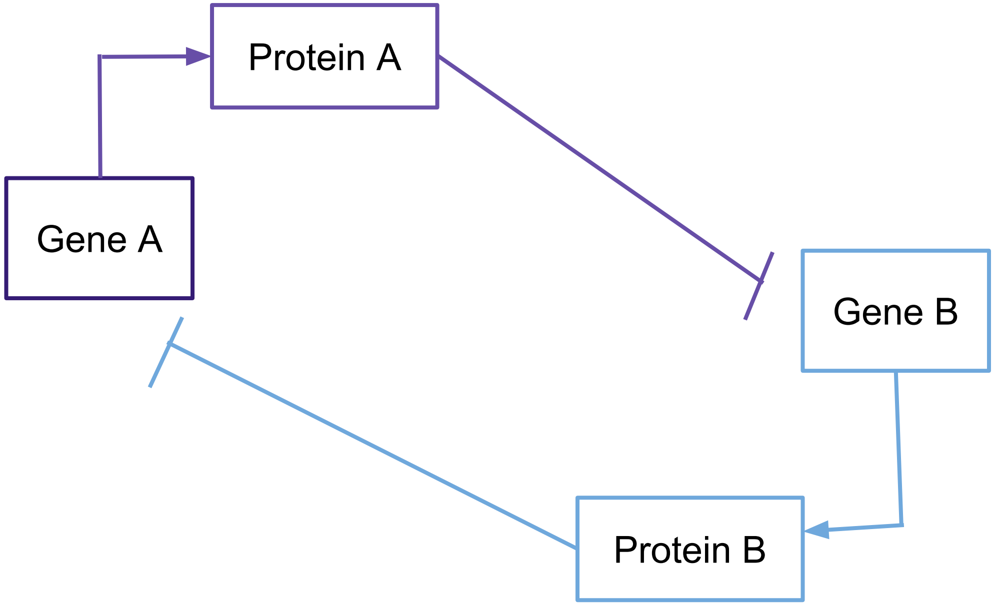
Synthetic Biology



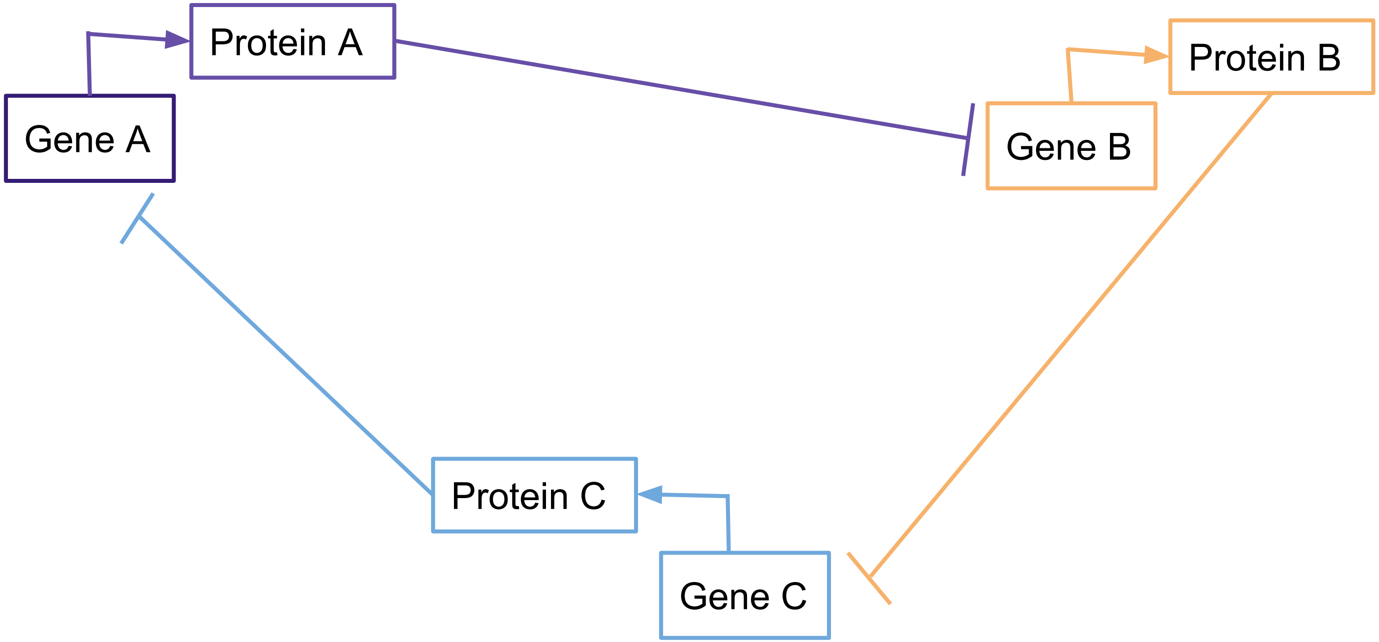
The Central Dogma of Biology



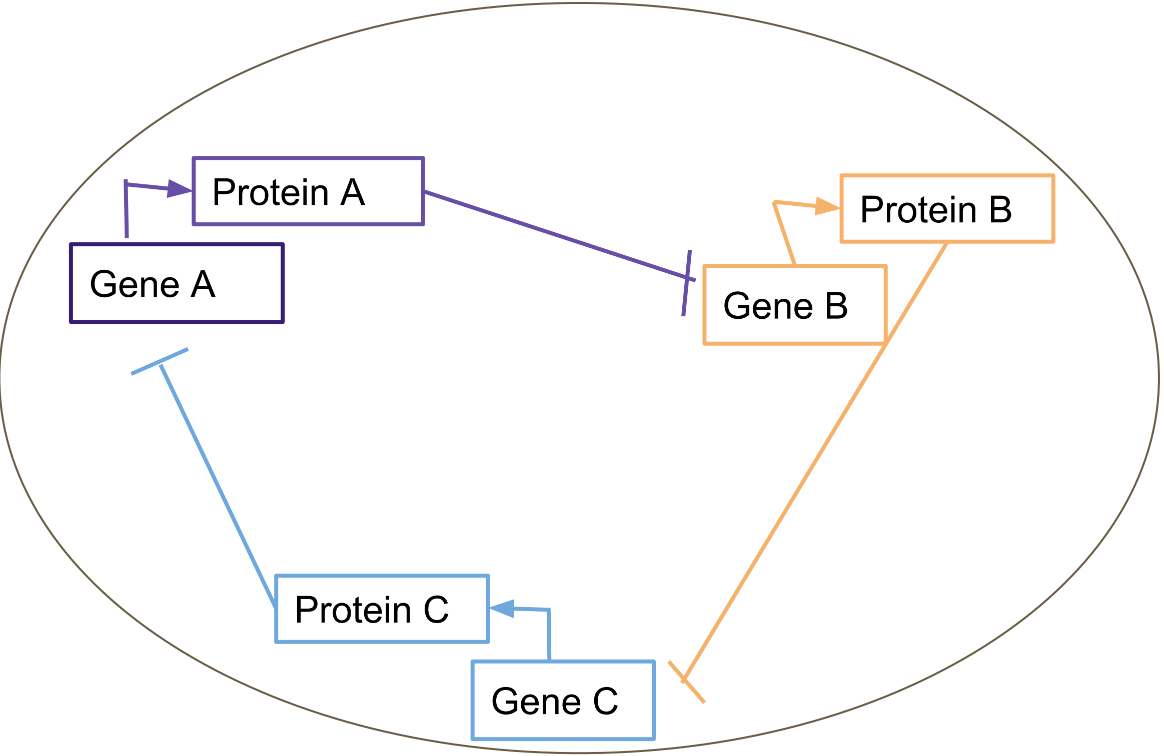
Integrated Gene Circuits: The Toggle Switch



The Repressilator System



The Repressilator System



In a single cell

Assumptions

- Stable temperature
  - Temperature affects binding and decay rates
- Closed system
  - No protein or mRNA leaving/entering the system

The Repressilator System: General Form

Rate of Change of the mRNA Concentration

$$\frac{da}{dt} = -k_{dm}a + \frac{\alpha}{1 + C^n}$$

Rate of Change of Protein Concentration

$$\frac{dA}{dt} = \beta a - k_{dp}A$$

- **a**: [mRNA a]
- **A**: [protein A]
- **C**: [protein C]
  - represses TX of gene A

Following parameters same for all species:

- $\mathbf{k_{dm}}$: mRNA deg.
- **α**: TX rate
- **n:** Hill's coefficient
- $\mathbf{k_{dp}}$: protein deg.
- **β**: TL rate

The Repressilator System: For All 3 Genes

Rate of Change of the mRNA Concentration

$$\frac{da}{dt} = -k_{dm}a + \frac{\alpha}{1 + C^n}$$

$$\frac{db}{dt} = -k_{dm}b + \frac{\alpha}{1 + A^n}$$

$$\frac{dc}{dt} = -k_{dm}c + \frac{\alpha}{1 + B^n}$$

Rate of Change of Protein Concentration

$$\frac{dA}{dt} = \beta a - k_{dp}A$$

$$\frac{dB}{dt} = \beta b - k_{dp}B$$

$$\frac{dC}{dt} = \beta c - k_{dp}C$$

The Repressilator System: Initial Conditions

Initial mRNA Concentrations

$$a(t=0)=1$$
$$b(t=0)=0$$
$$c(t=0)=0$$

Initial Protein Concentrations

$$A(t=0)=0$$
$$B(t=0)=0$$
$$C(t=0)=0$$

Parameter Values

$$\alpha=100$$
$$n=2$$
$$k_{dm}=1$$
$$\beta=1$$
$$k_{dp}=1$$

Numerical Method - Explicit Runge-Kutta (RK4)

$$y_{n+1} = y_n + \phi h$$

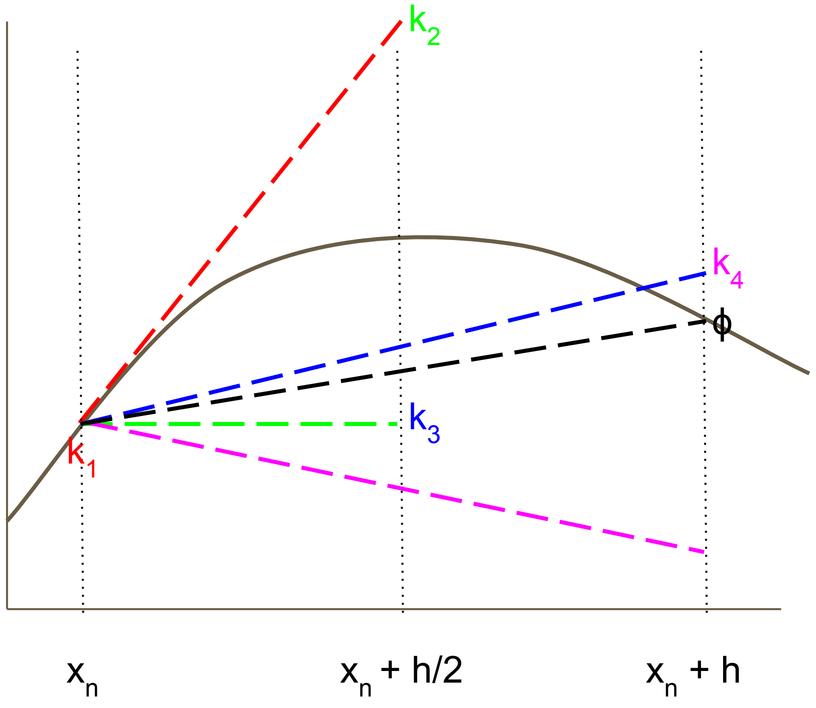
$$k_1 = hf\left(x_n, y_n\right)$$

$$k_2 = hf\left(x_n + \frac{1}{2}h, y_n + \frac{1}{2}k_1 h\right)$$

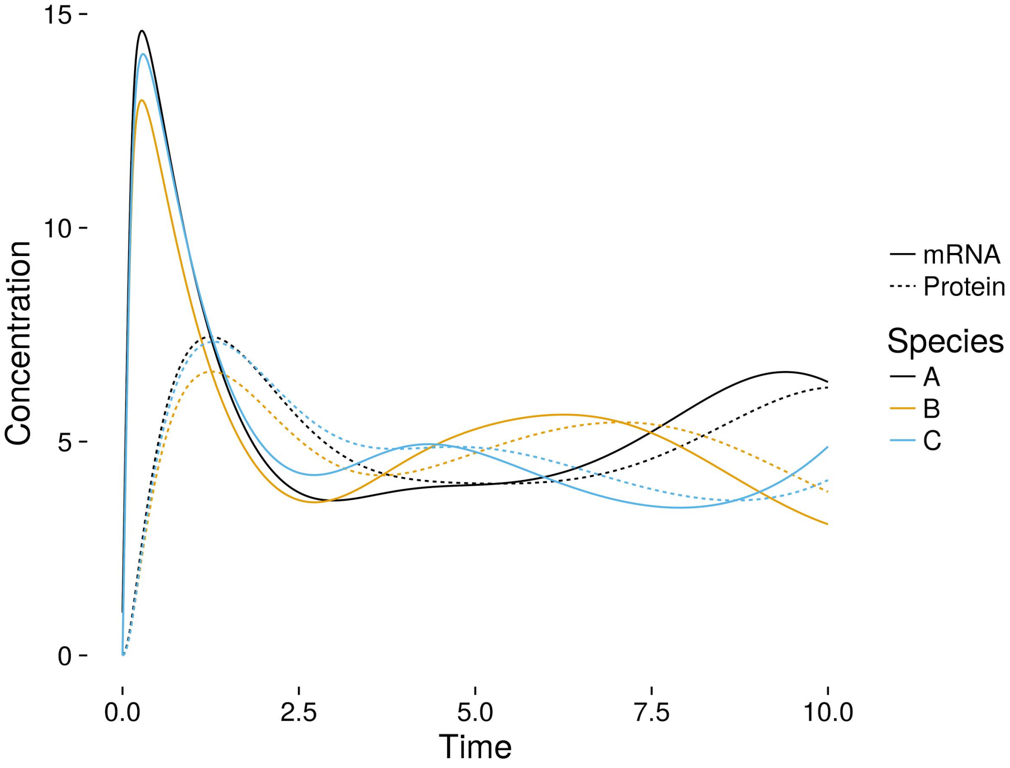
$$k_3 = hf\left(x_n + \frac{1}{2}h, y_n + \frac{1}{2}k_2 h\right)$$

$$k_4 = hf\left(x_n + h, y_n + k_3 h\right)$$

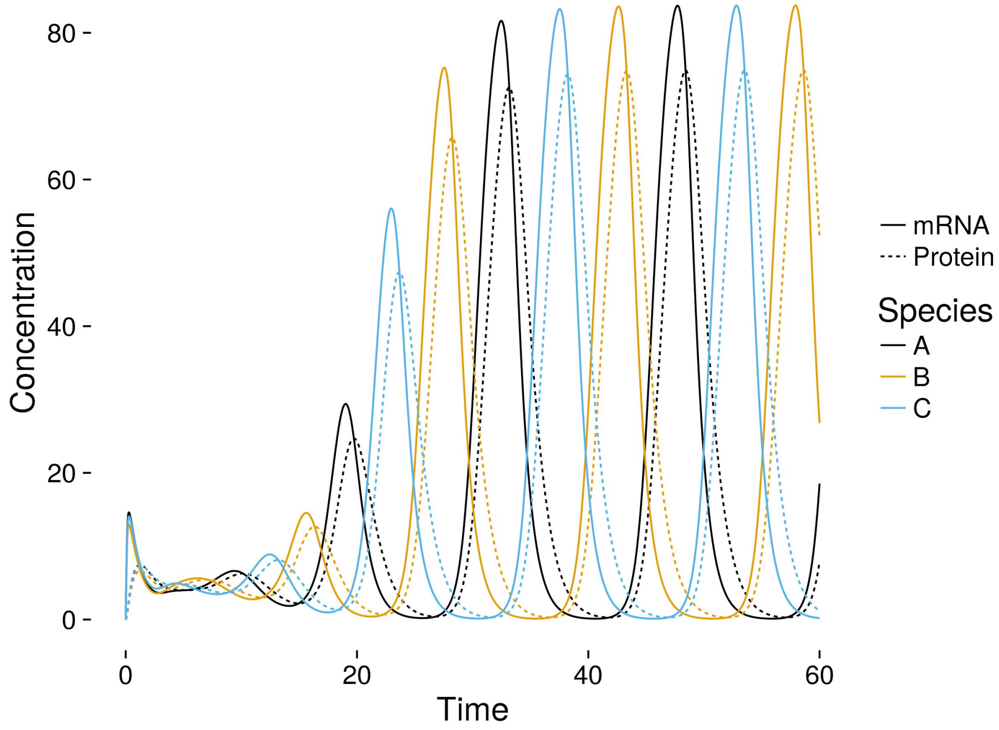
$$y_{n+1} = y_n + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

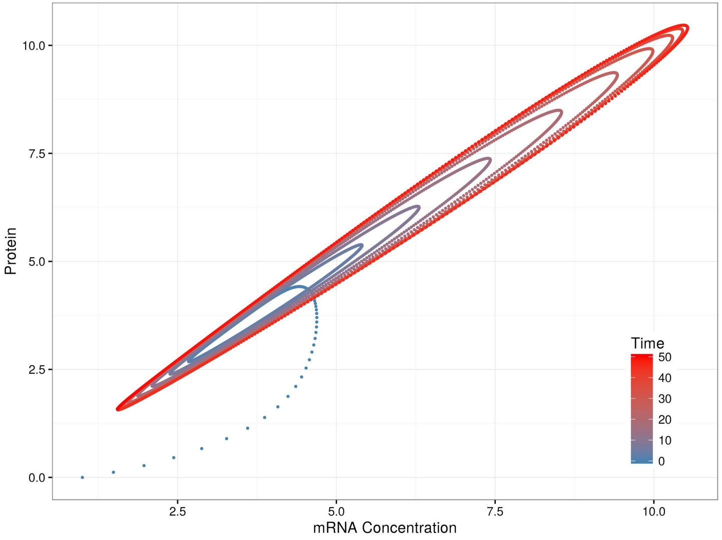


Repressilator - Starting times



Repressilator - Steady State





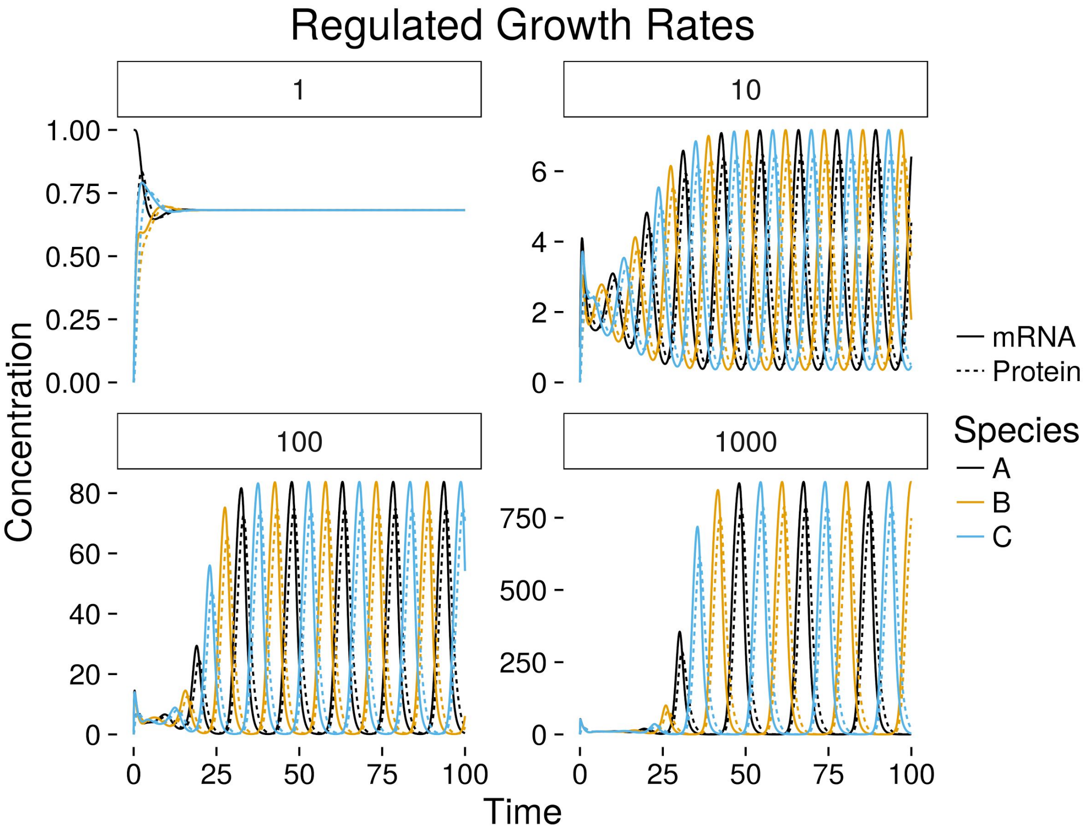
Modulating Regulated Transcription Rate (α)

Rate of Change of the mRNA Concentration

$$\frac{da}{dt} = -k_{deg}a + \frac{\boxed{\alpha}}{1 + C^n}$$

$$\frac{db}{dt} = -k_{deg}b + \frac{\boxed{\alpha}}{1 + A^n}$$

$$\frac{dc}{dt} = -k_{deg}c + \frac{\boxed{\alpha}}{1 + B^n}$$



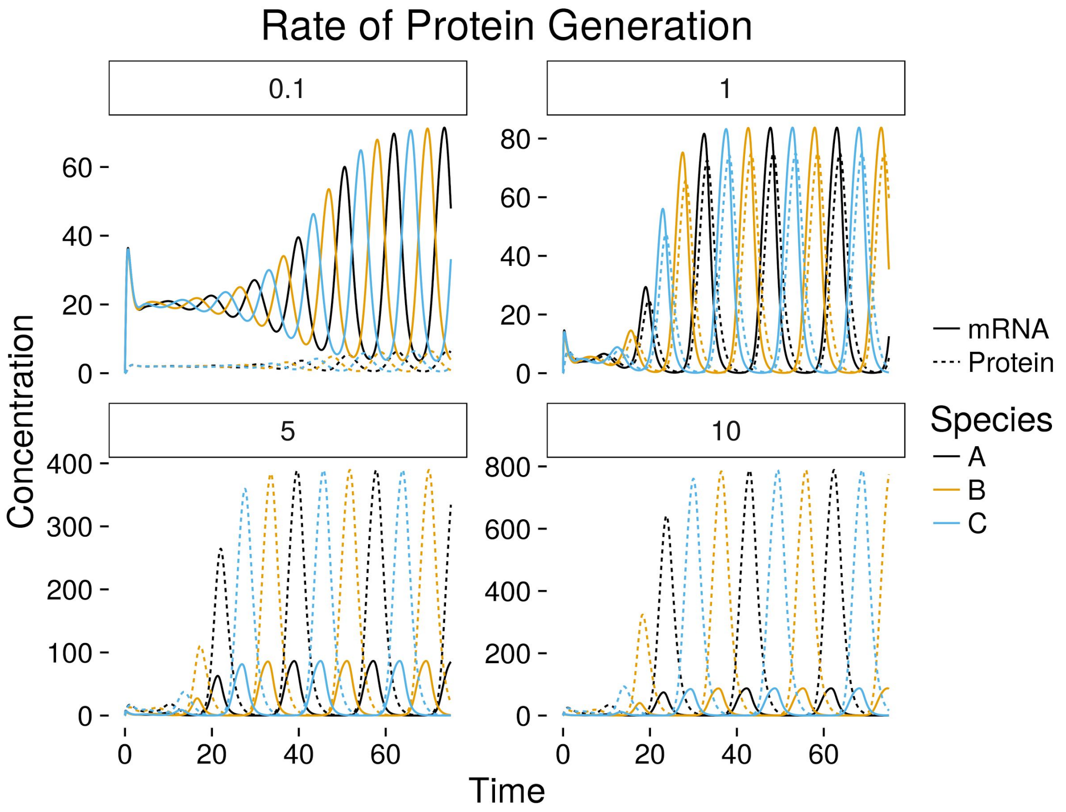
Modulating Translation (β)

Rate of Change of Protein Concentration

$$\frac{dA}{dt} = \beta a - k_{dp} A$$

$$\frac{dB}{dt} = \beta b - k_{dp} B$$

$$\frac{dC}{dt} = \beta c - k_{dp} C$$



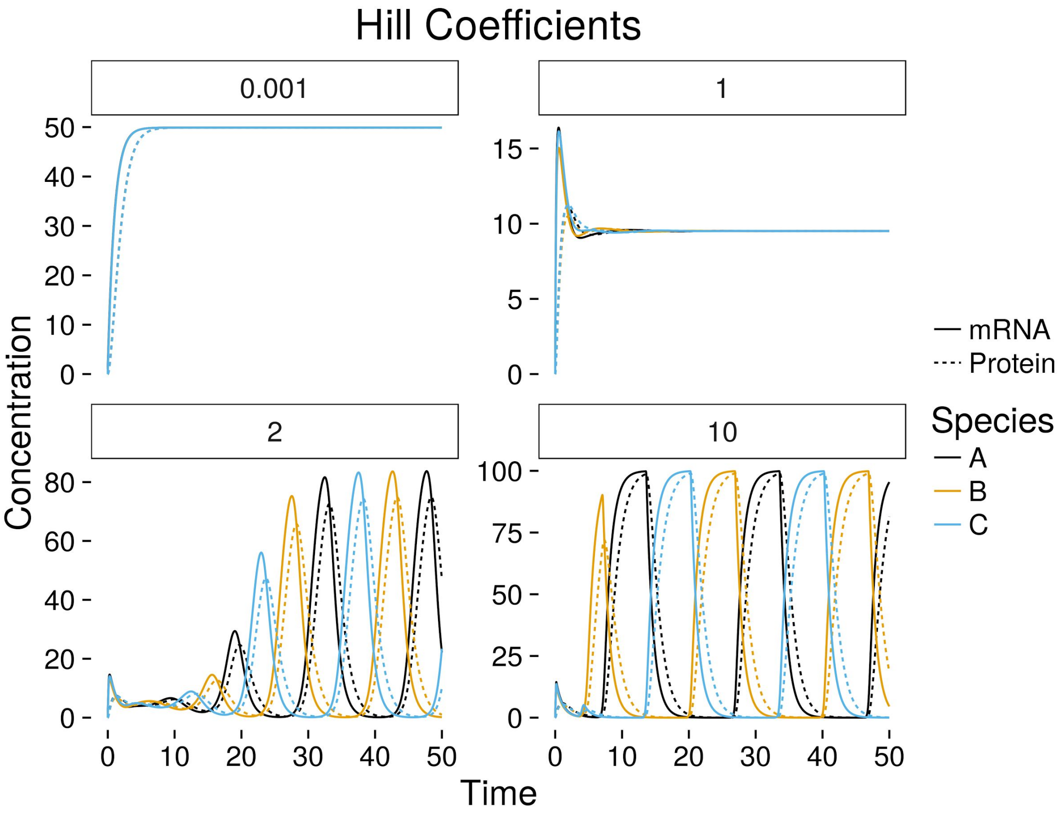
Modulating Cooperativity of Repressor and DNA

Rate of Change of the mRNA Concentration

$$\frac{da}{dt} = -k_{deg}a + \frac{\alpha}{1 + C^{n}}$$

$$\frac{db}{dt} = -k_{deg}b + \frac{\alpha}{1 + A^{n}}$$

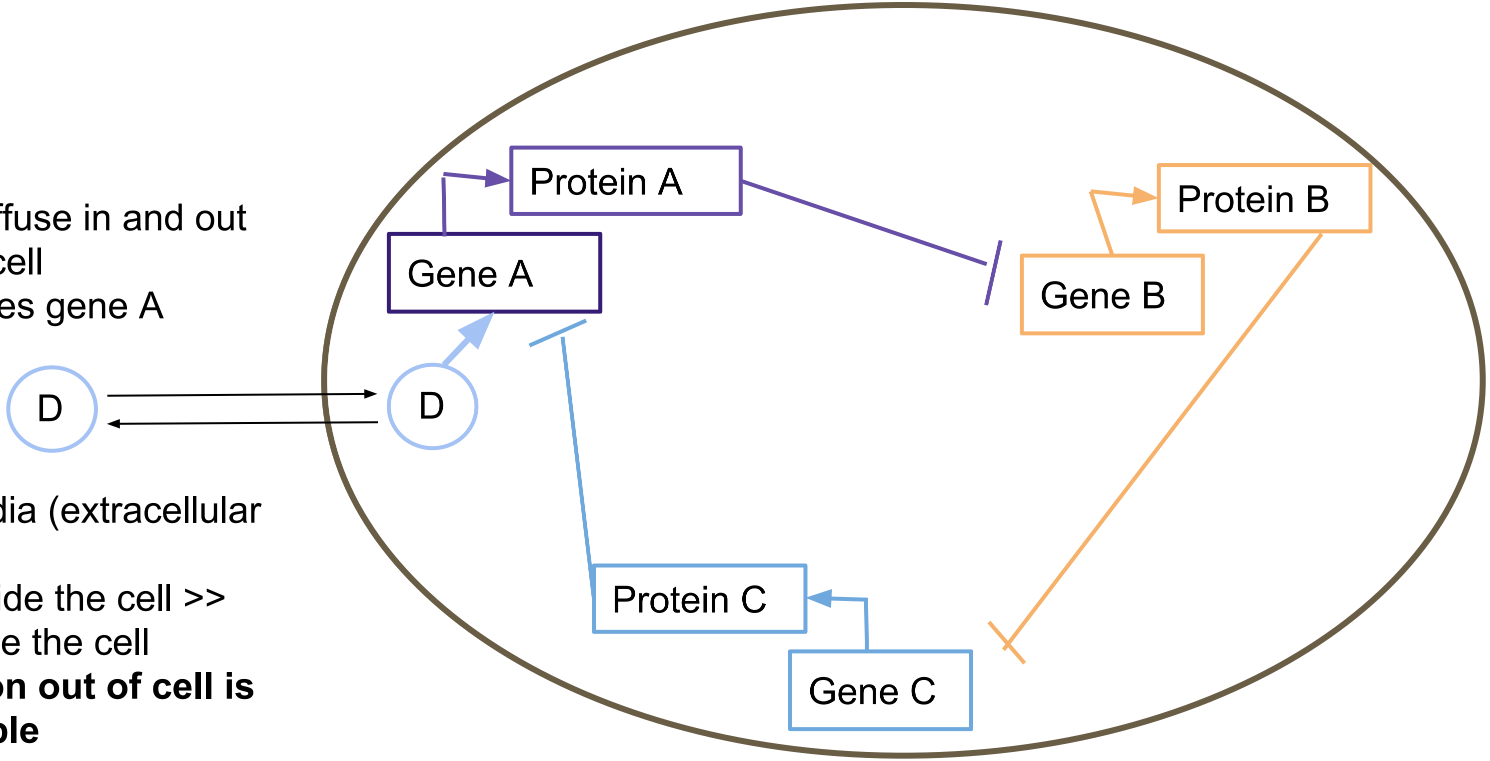
$$\frac{dc}{dt} = -k_{deg}c + \frac{\alpha}{1 + B^{n}}$$



The Repressilator System with a Drug Inducer

New Parameter

- D = drug
  - Can diffuse in and out of the cell
  - Activates gene A



A single cell

Assumptions

- Spike the media (extracellular fluid) with D
  - [D] outside the cell >> [D] inside the cell
  - **Diffusion out of cell is negligible**

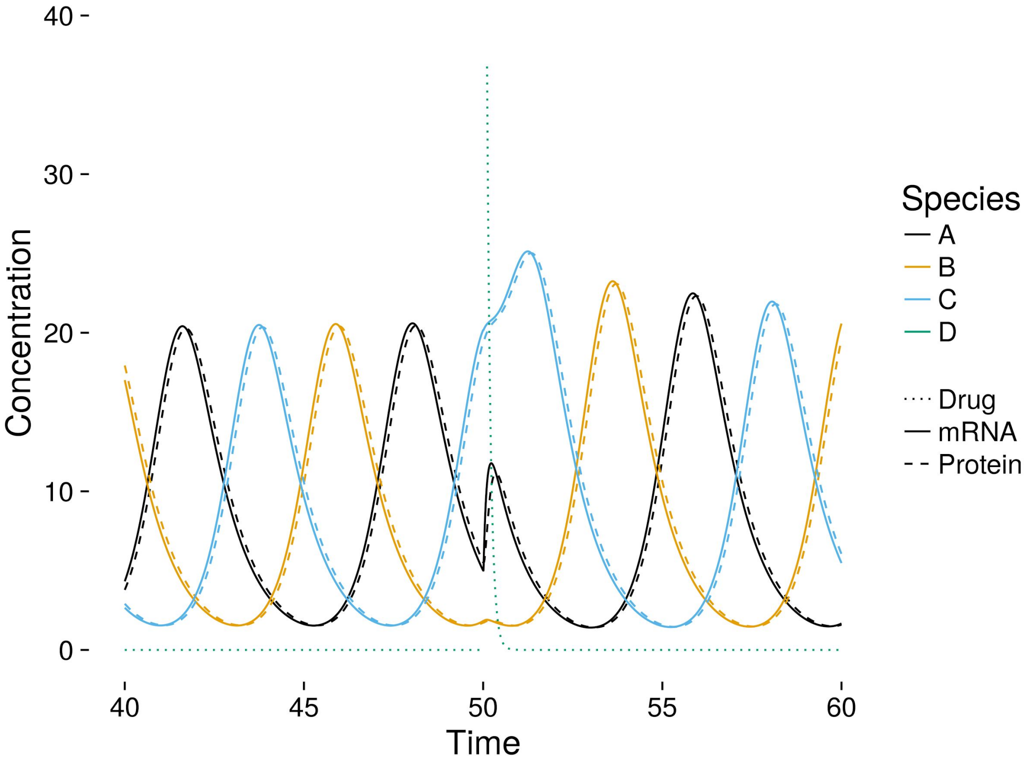
The Repressilator System with a Drug Inducer

Rate of Change of the mRNA Concentration

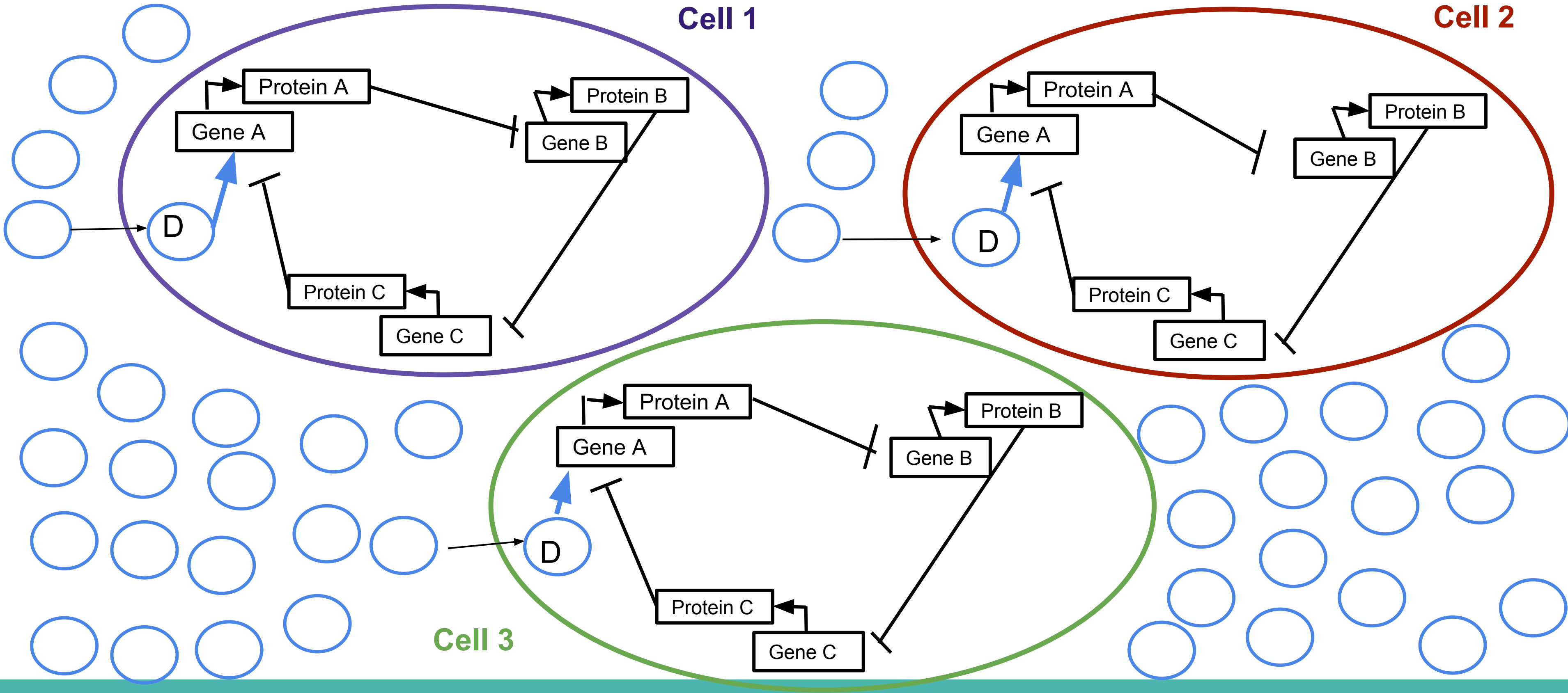
$$\frac{da}{dt} = -k_{dm}a + \frac{\alpha}{1 + C^n} + kD$$

$$\frac{db}{dt} = -k_{dm}b + \frac{\alpha}{1 + A^n}$$

$$\frac{dc}{dt} = -k_{dm}c + \frac{\alpha}{1 + B^n}$$



The Repressilator System & Synchronization



The Repressilator: 3 Cell System (i=1,2,3)

mRNA concentrations: a, b, c

$$\frac{da_i}{dt} = -k_{dm}a_i + \frac{\alpha}{1 + C_i^n} + kD$$

$$\frac{db_i}{dt} = -k_{dm}b_i + \frac{\alpha}{1 + A_i^n}$$

$$\frac{dc_i}{dt} = -k_{dm}c_i + \frac{\alpha}{1 + B_i^n}$$

Protein concentrations: A, B, C & Drug concentration

$$\frac{dA_i}{dt} = \beta a_i - k_{dp}A_i$$

$$\frac{dB_i}{dt} = \beta b_i - k_{dp}B_i$$

$$\frac{dC_i}{dt} = \beta c_i - k_{dp}C_i$$

$$\frac{dD}{dt} = -k_{dd}D$$

The Repressilator: 3 Cell System Initial Conditions

Cell 1

$$a_1(t=0)=1$$
$$b_1(t=0)=0$$
$$c_1(t=0)=0$$

Cell 2

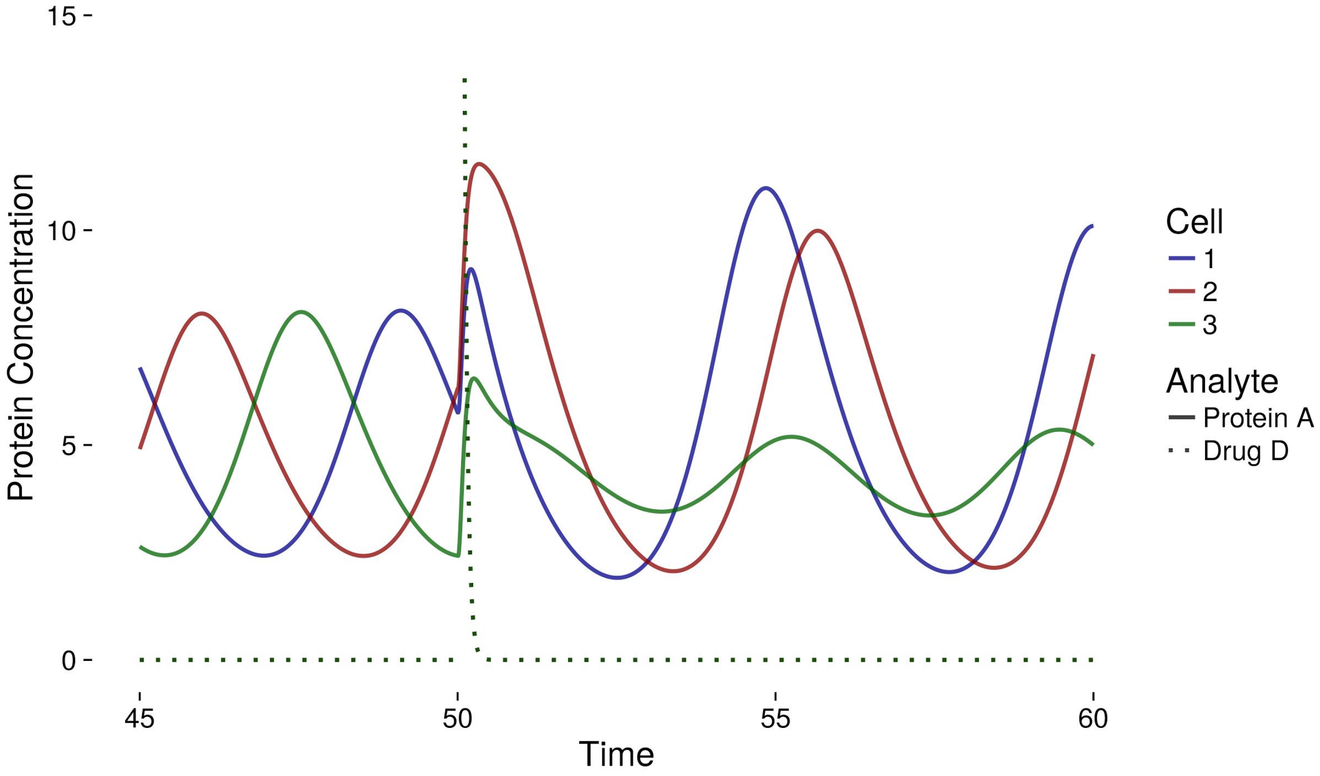
$$a_2(t=0)=0$$
$$b_2(t=0)=1$$
$$c_2(t=0)=0$$

Cell 3

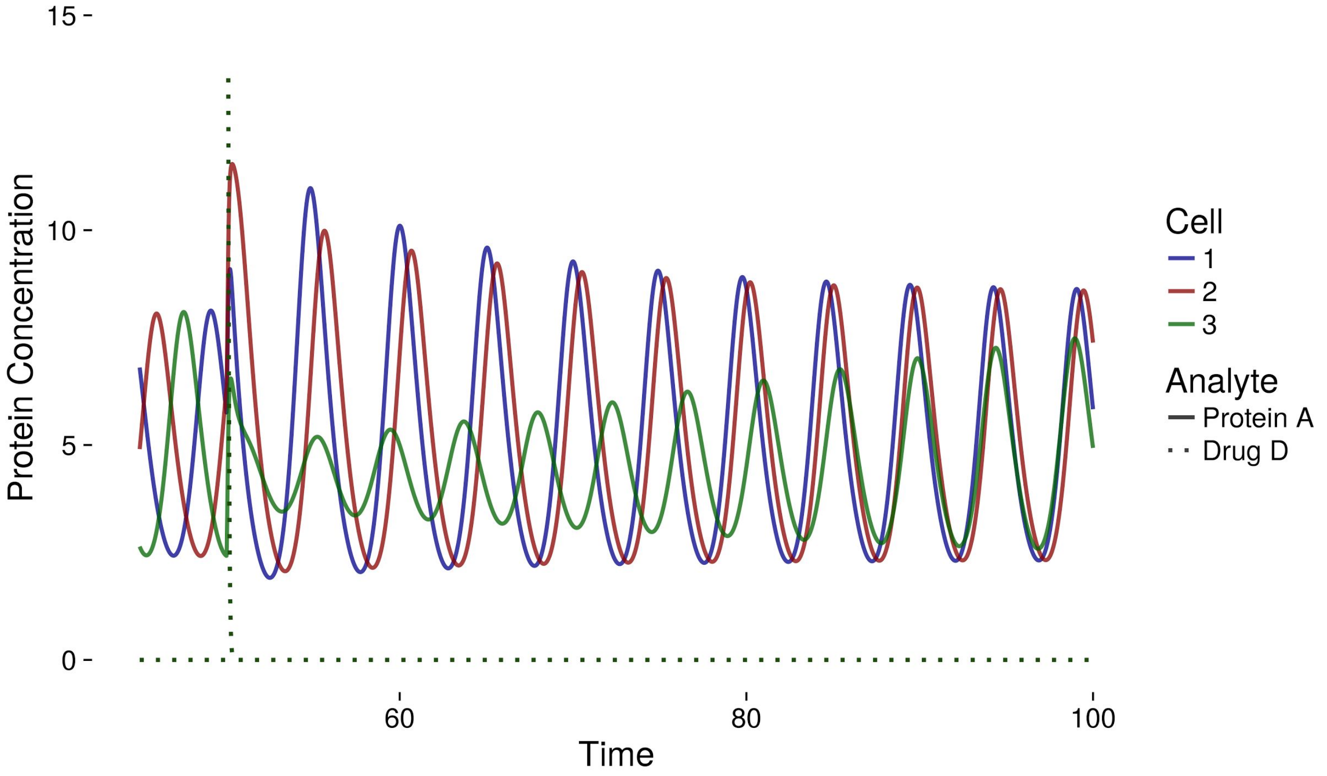
$$a_3(t=0)=0$$
$$b_3(t=0)=0$$
$$c_3(t=0)=1$$

$A(t=0)=B(t=0)=C(t=0)=0$ for all cells

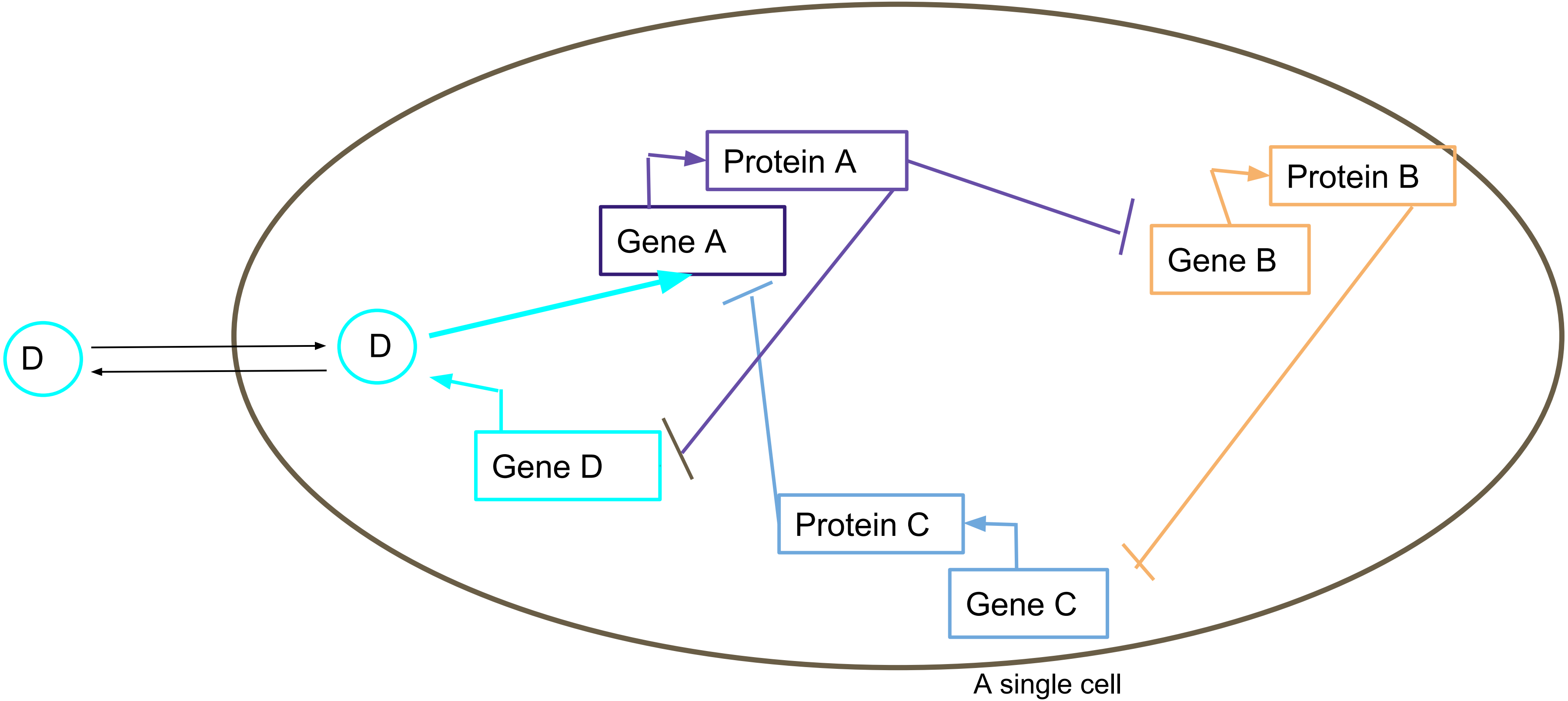
Repressilator with Sensing - 3 cell synchronization



Repressilator with Sensing - 3 cell synchronization



The Repressilator System: Adding Complexity



Quorum Sensing: Adding Even More Complexity

Extra Slides

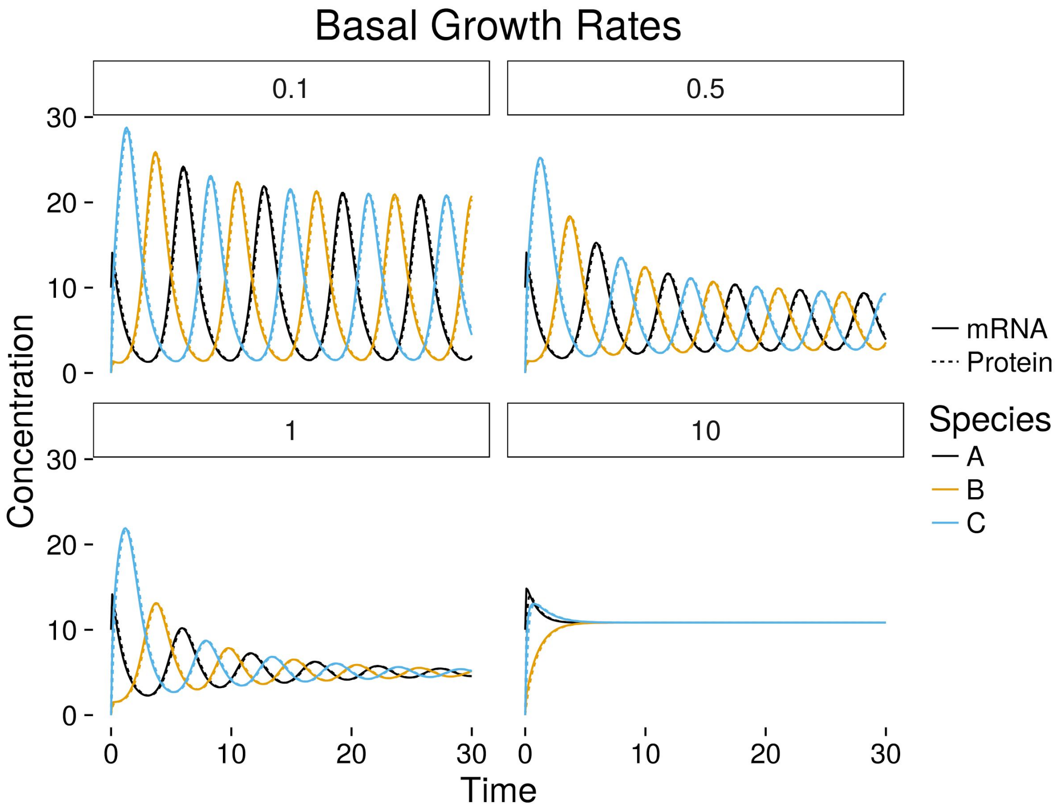
The Effect of Basal Transcription Rate (α_0)

Rate of Change of the mRNA Concentration

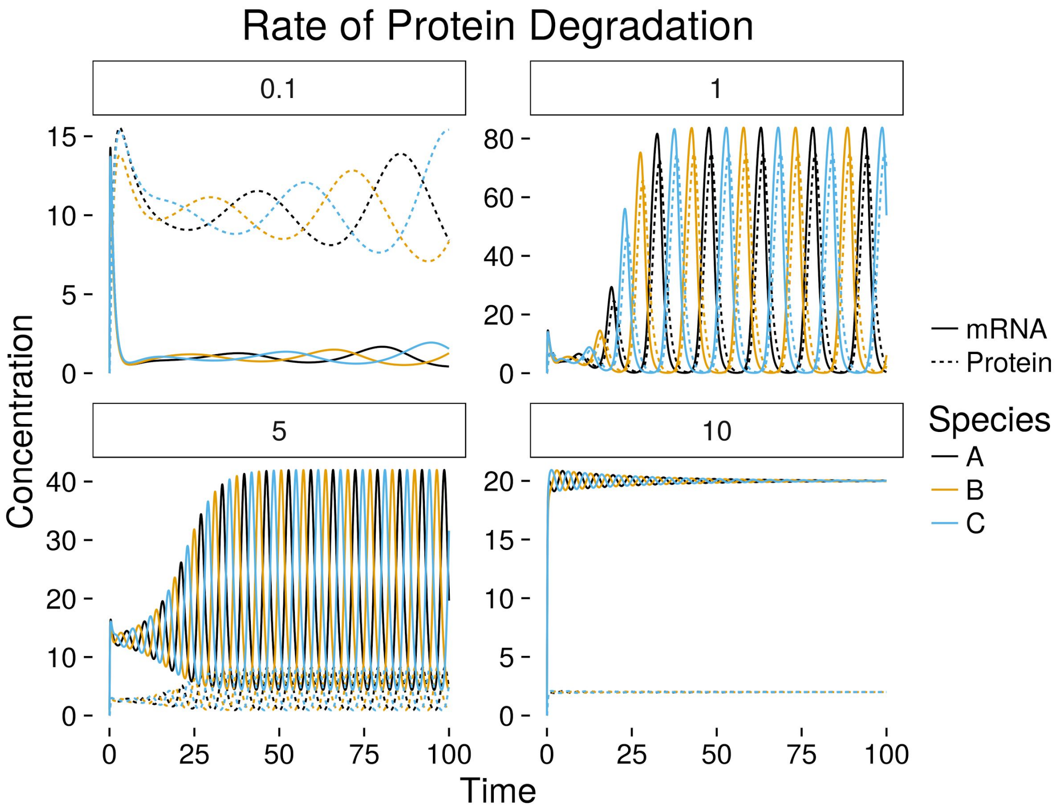
$$\frac{da}{dt} = -k_{deg}a + \frac{\alpha}{1 + C^n} + \boxed{\alpha_0}$$

$$\frac{db}{dt} = -k_{deg}b + \frac{\alpha}{1 + A^n} + \boxed{\alpha_0}$$

$$\frac{dc}{dt} = -k_{deg}c + \frac{\alpha}{1 + B^n} + \boxed{\alpha_0}$$



The Effect of Protein Degradation



Coupled RK4

$$\frac{dy_1}{dt} = f_1(t, y_1, y_2),$$
$$\frac{dy_2}{dt} = f_2(t, y_1, y_2),$$

$$k_{1,1} = f_1(t_k, y_{1,k}, y_{2,k}),$$
$$k_{2,1} = f_2(t_k, y_{1,k}, y_{2,k}),$$
$$k_{1,2} = f_1(t_k + 0.5h, y_{1,k} + 0.5k_{1,1}h, y_{2,k} + 0.5k_{2,1}h),$$
$$k_{2,2} = f_2(t_k + 0.5h, y_{1,k} + 0.5k_{1,1}h, y_{2,k} + 0.5k_{2,1}h),$$
$$k_{1,3} = f_1(t_k + 0.5h, y_{1,k} + 0.5k_{1,2}h, y_{2,k} + 0.5k_{2,2}h),$$
$$k_{2,3} = f_2(t_k + 0.5h, y_{1,k} + 0.5k_{1,2}h, y_{2,k} + 0.5k_{2,2}h),$$
$$k_{1,4} = f_1(t_k + h, y_{1,k} + k_{1,3}h, y_{2,k} + k_{2,3}h),$$
$$k_{2,4} = f_2(t_k + h, y_{1,k} + k_{1,3}h, y_{2,k} + k_{2,3}h),$$
$$y_{1,k+1} = y_{1,k} + \frac{h}{6}(k_{1,1} + 2k_{1,2} + 2k_{1,3} + k_{1,4}),$$
$$y_{2,k+1} = y_{2,k} + \frac{h}{6}(k_{2,1} + 2k_{2,2} + 2k_{2,3} + k_{2,4}).$$