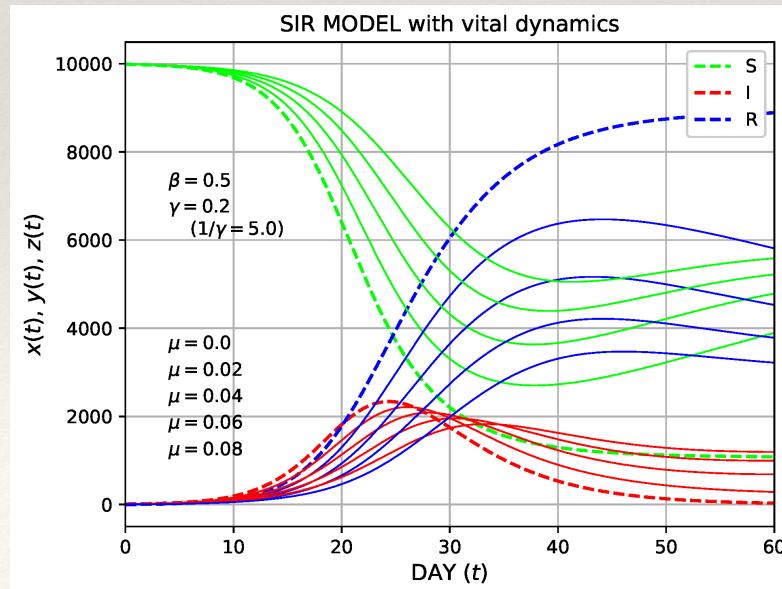
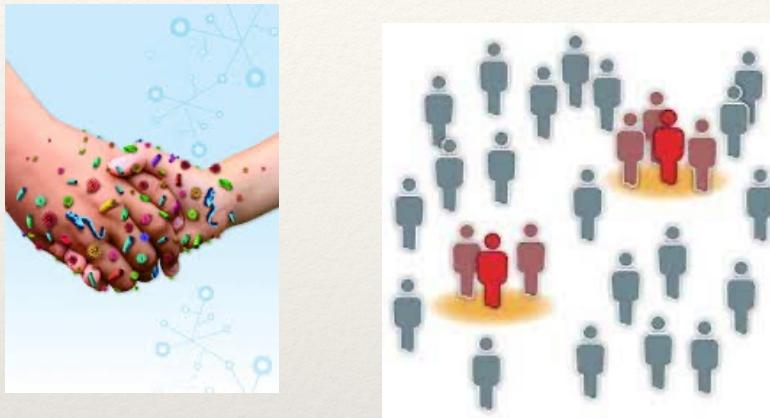

Modelling in Computational Science, BERN01, 7.5hp

Practical and theoretical
knowledge of numerical
methods used for solving
ODE modells for real Life
Science problems.

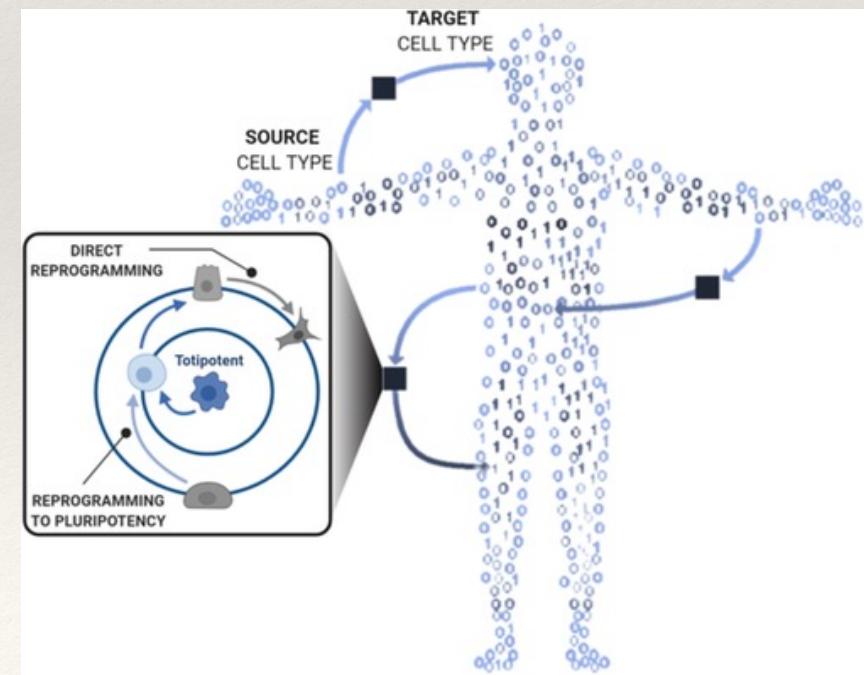
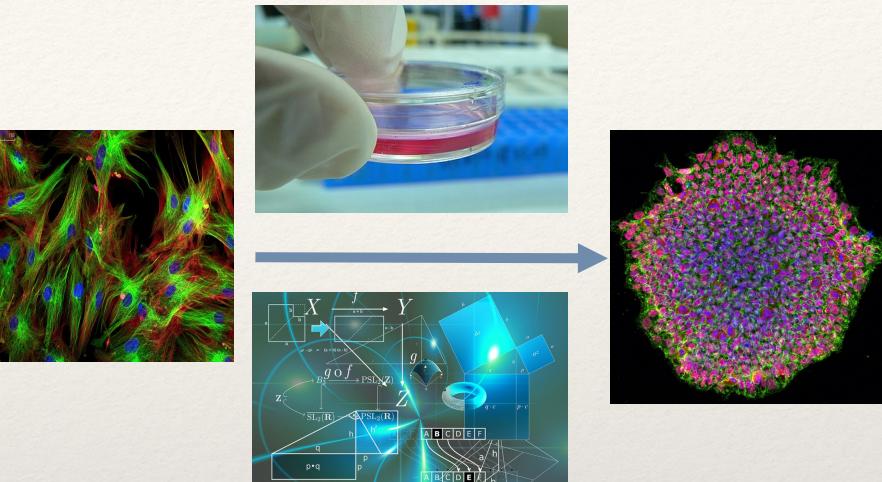
1st study period, autumn semester

Projects

Disease spreading



Cell Reprogramming



Disease Spreading



The SIS Model –heuristic derivation

Two categories:

- $S = S(t)$ is the number of susceptible members of the population at time t
- $I = I(t)$ is the number of infected members of the population at time t.

$$N = S + I - \text{total population size}$$

Consider the time interval $[t, t+\Delta t]$

The probability that an infected transmits the disease to a susceptible is proportional with Δt :

$$P = \Delta t \cdot \sigma \cdot T \cdot \frac{S}{N}$$

- σ is the number of contacts per units time between individuals - region dependent
 - T is the infection probability for each contact – disease dependent
 - S/N is the probability that the contact is with a susceptible (rather than with an infected)
- $\beta = \sigma \cdot T$ rate constant

Disease Spreading

The SIS Model –heuristic derivation $P = \Delta t \cdot \beta \cdot \frac{S}{N}$ probability to infect
Time evolution in interval Δt for infected α – is the recovery rate

$$I(t+\Delta t) = I(t) + \Delta t \beta \frac{S}{N} I(t) - \Delta t \alpha I(t) \rightarrow \text{move } I(t) \text{ to the left}$$

divide by Δt

$$\frac{I(t+\Delta t) - I(t)}{\Delta t} = \beta \frac{S}{N} I(t) - \alpha I(t) \rightarrow I(t) = I$$
$$\frac{dI}{dt} = \beta \frac{SI}{N} - \alpha I$$

Time evolution in interval Δt for susceptible

$$S(t+\Delta t) = S(t) - \Delta t \beta \frac{S}{N} I(t) + \Delta t \alpha I(t) \rightarrow$$

$$\frac{S(t+\Delta t) - S(t)}{\Delta t} = -\beta \frac{S}{N} I(t) + \alpha I(t) \rightarrow$$
$$\frac{dS}{dt} = -\beta \frac{SI}{N} + \alpha I$$



Disease Spreading



Literature

D. Brockmann, et al. Human Mobility and Spatial Disease Dynamics, Diffusion Fundamentals III, Leipziger Universitätsverlag (2009)1, <http://rocs.northwestern.edu/publications/>
M. Keeling, Mathematical Epidemiology, http://www.warwick.ac.uk/~masfz/Teaching_index.html



The SIS Model

$$\frac{dI}{dt} = \beta \frac{SI}{N} - \alpha I$$

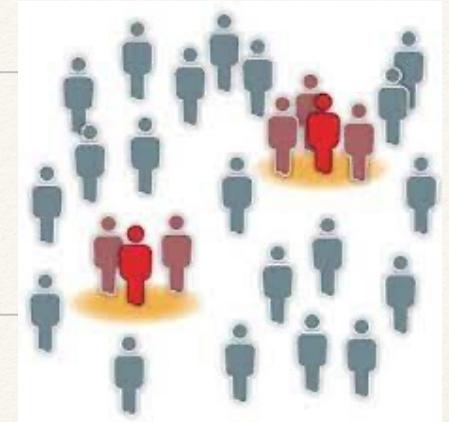
$$\frac{dS}{dt} = -\beta \frac{SI}{N} + \alpha I$$

- $\beta \frac{SI}{N}$ is the infection of susceptible with rate β
- αI – recovery of infected with rate α
- $N = S + I$ – total population size,

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} = 0$$

The total population stays constant
Death not considered in SIS model

Disease Spreading



The SIR Model

Extends the SIS model by adding a category – $R(t)$ = recovered and immune

For this model the total population is $N=S+I+R$

The rates are:

β - rate of infection of susceptible

α – rate of recovery of infected

γ – vaccination of susceptibles turning S into R

$$\frac{dS}{dt} = -\beta \frac{SI}{N} - \gamma S$$

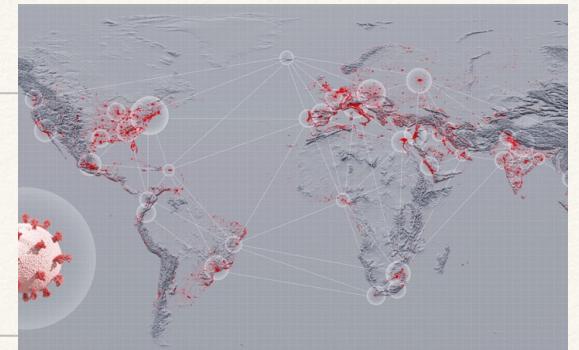
$$\frac{dI}{dt} = \beta \frac{SI}{N} - \alpha I$$

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0$$

$$\frac{dR}{dt} = \gamma S + \alpha I$$

Total population is constant

Disease Spreading



The SIR Model - with travelling

Extends the SIR model to take into consideration mobility

$$\frac{dS_n}{dt} = -\beta \frac{S_n I_n}{N} - \gamma S_n + \sum_{m \neq n} (w_{n \leftarrow m} S_m - w_{m \leftarrow n} S_n)$$

$$\frac{dI_n}{dt} = \beta \frac{S_n I_n}{N} - \alpha I_n + \sum_{m \neq n} (w_{n \leftarrow m} I_m - w_{m \leftarrow n} I_n)$$

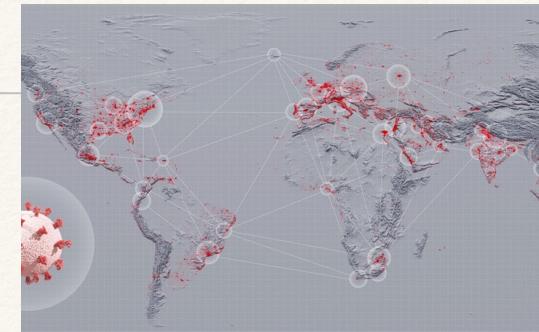
$$\frac{dR_n}{dt} = \gamma S_n + \alpha I_n + \sum_{m \neq n} (w_{n \leftarrow m} R_m - w_{m \leftarrow n} R_n)$$

$N_n = S_n + I_n + R_n$ size of population n. Constant if travel is balanced.

$w_{n \leftarrow m}$ the probability per unit time that a random person in population m travels to pop. n

$w_{n \leftarrow m} I_m$ shows how many infected in population m travel to population n per unit time

Disease Spreading



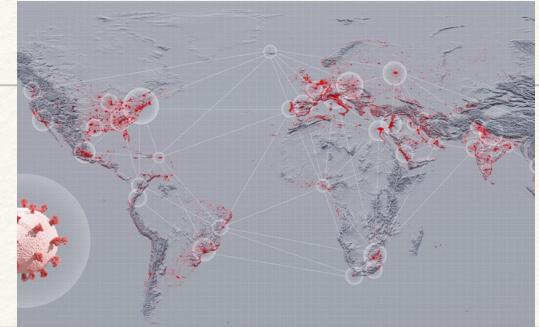
In this project you will solve model equations describing the time-evolution of healthy and infected people in connected populations.

Different strategies for minimizing effects of a disease, such as vaccination, should be studied.

Your job is:

1. choose your “favorite” disease and favorite cities
2. figure out, using “appropriate” sources, realistic parameters for that disease.
3. include realistic parameters for traveling dynamics between populations.
4. solve the appropriate rate equations numerically
5. investigate the effect of vaccination or quarantine on disease spreading patterns.

Disease Spreading



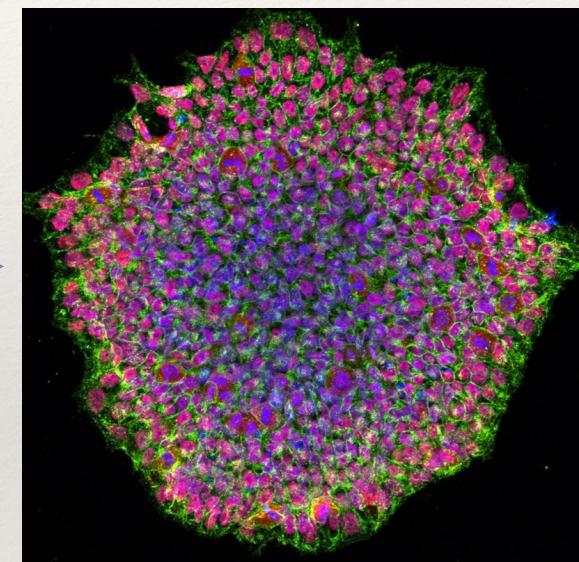
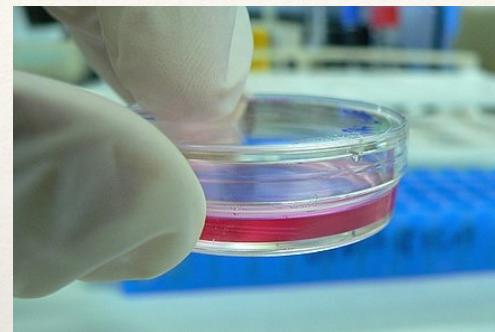
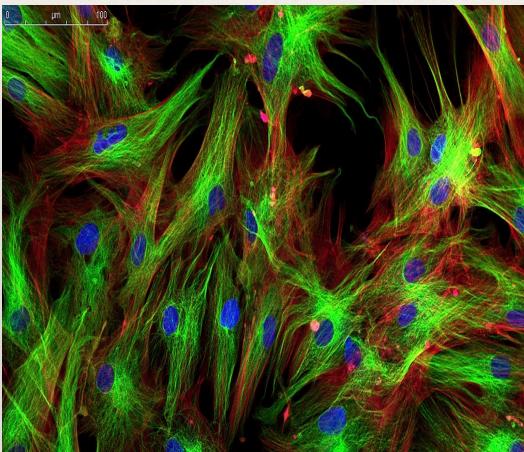
The project report for project Module A should contain:

- Description of the problem you have chosen to study.
- Describe and motivate the algorithm(s) you use.
- Estimate numerical errors.
- Results of simulations.
- Conclusions
- Appendix: Include a listing of your program.

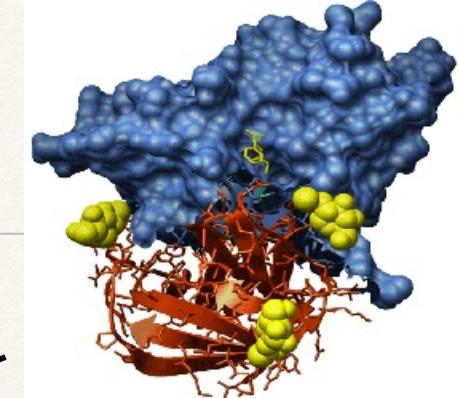
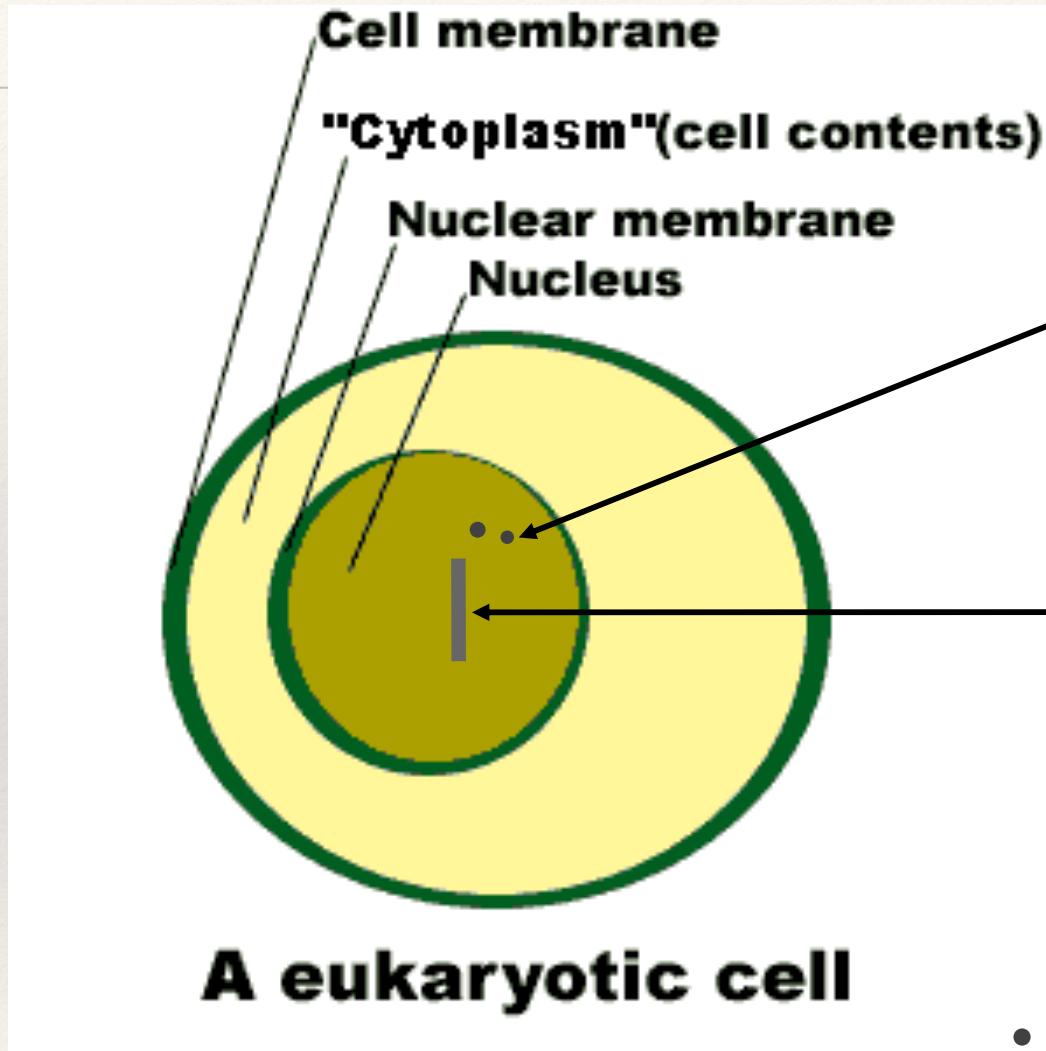
Pdf-format

Send your report before the deadline by e-mail to:
victor.olariu@cec.lu.se

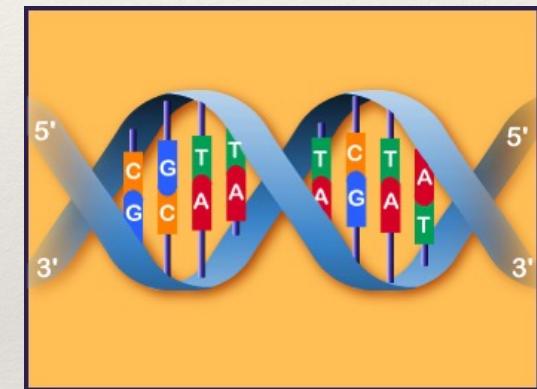
Cell Reprogramming



The Cell



Protein



DNA

- Human body has around ten trillions cells
300 different cell types

DNA Proteins

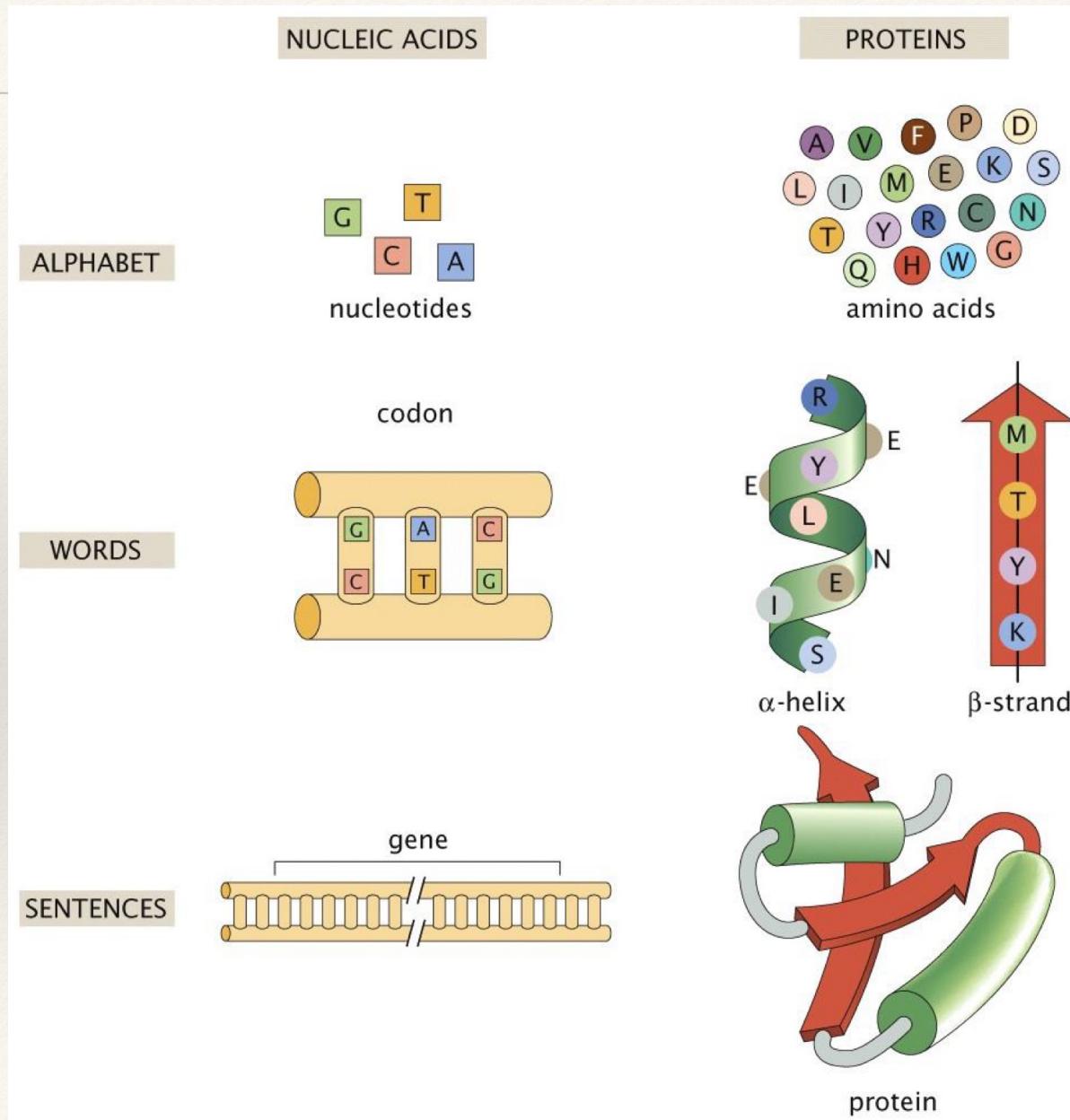
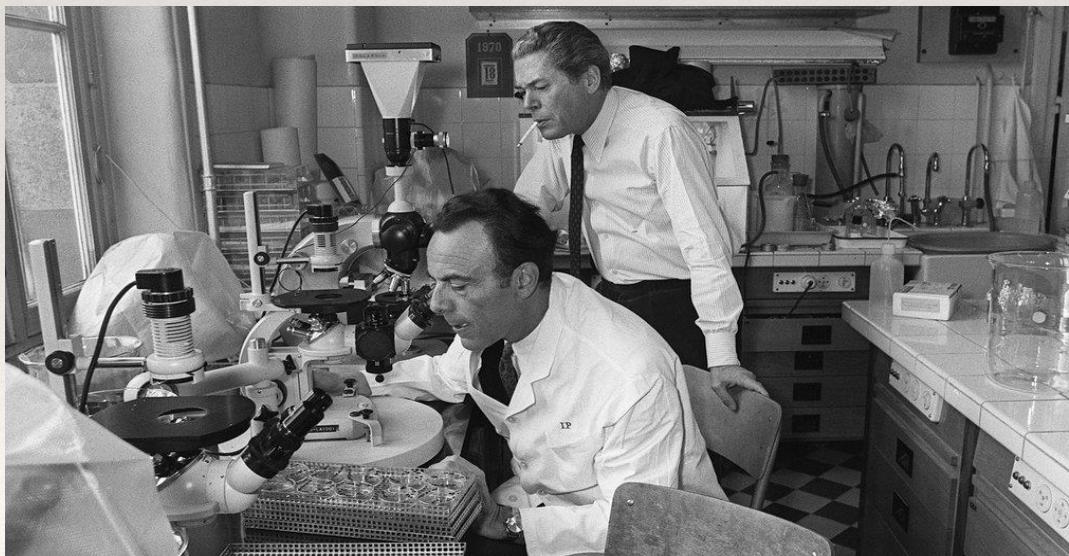
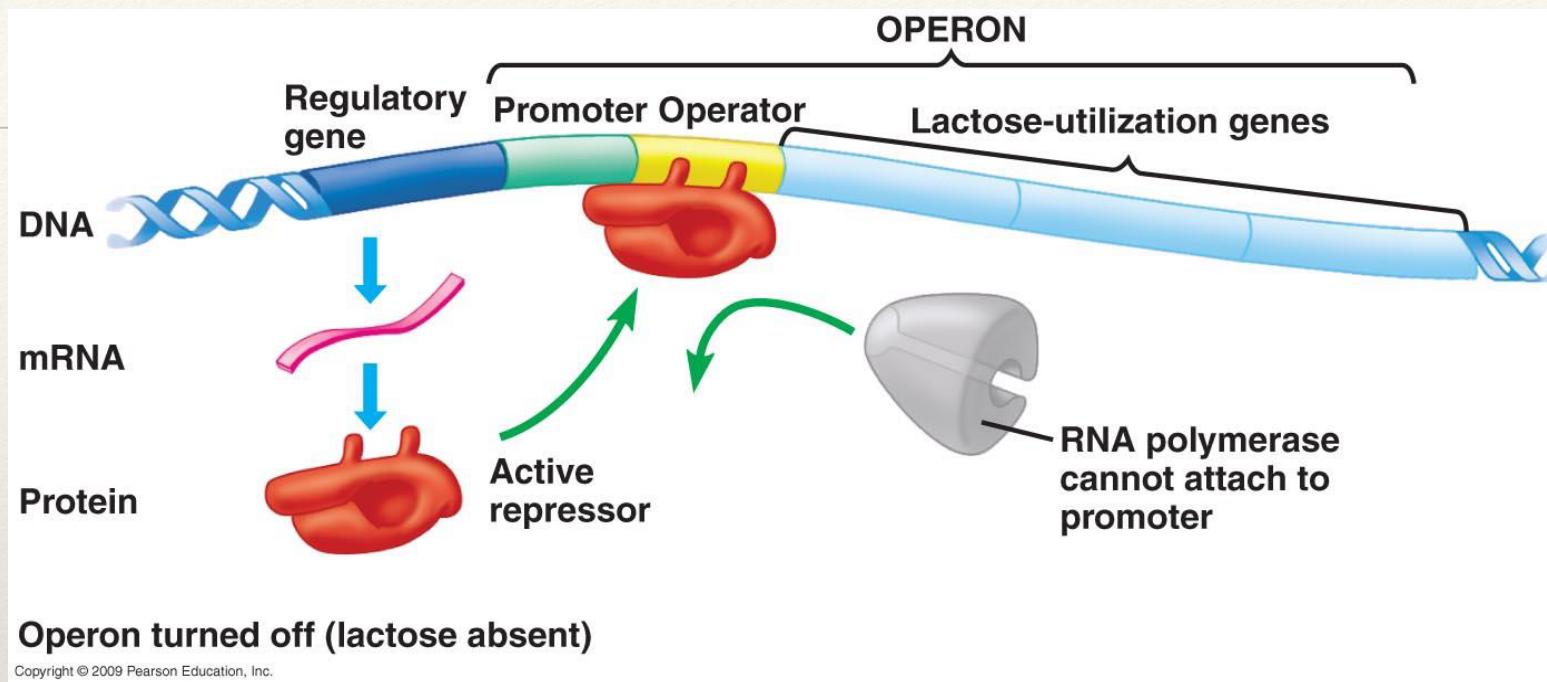


Figure 1.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Movie Transcription Translation

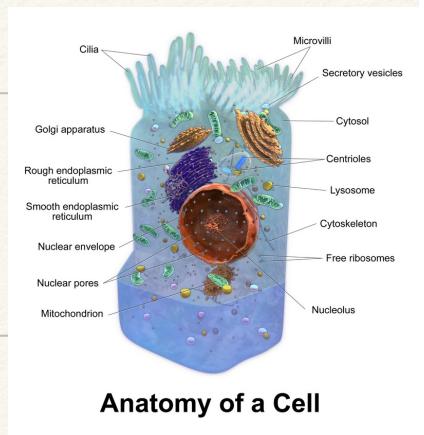
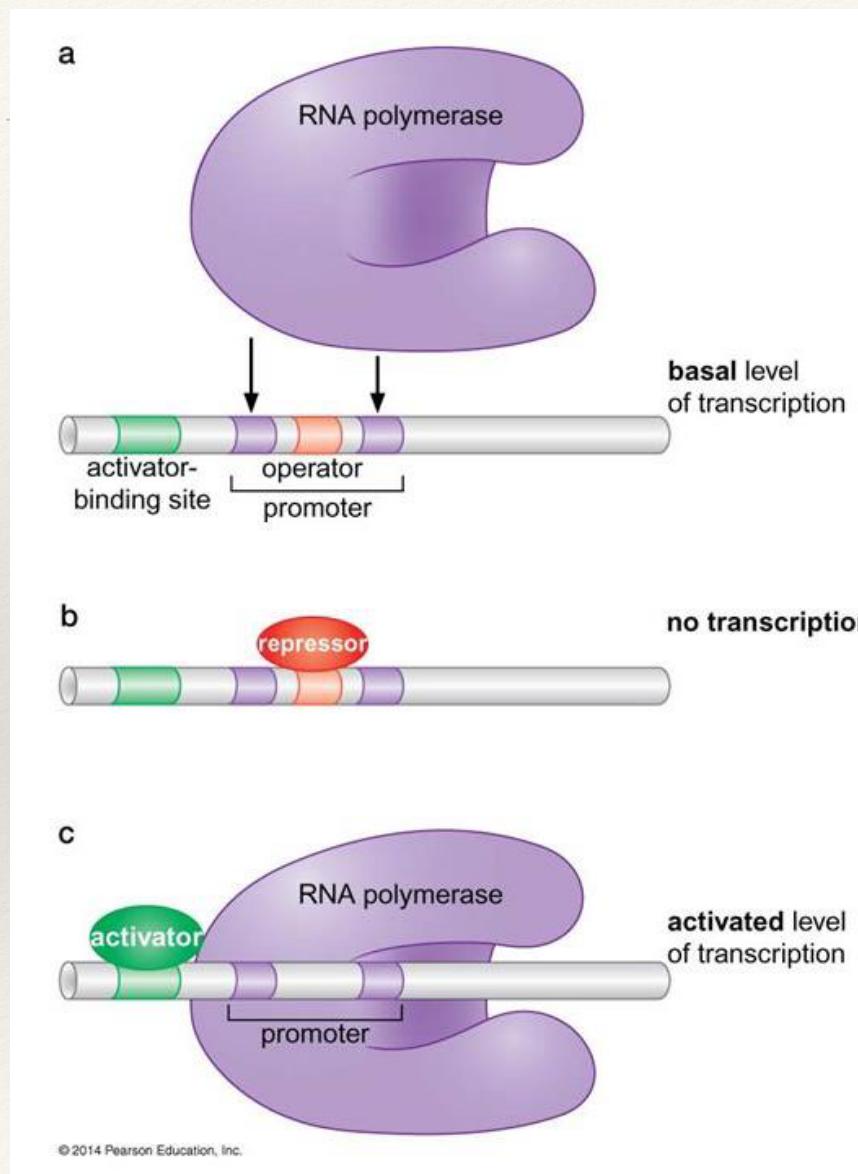


Gene Expression Is Regulated



Francois Jacob & Jaques Monod, 1961

Gene Expression Is Regulated



Transcription Factors



Michaelis-Menten – Transcription



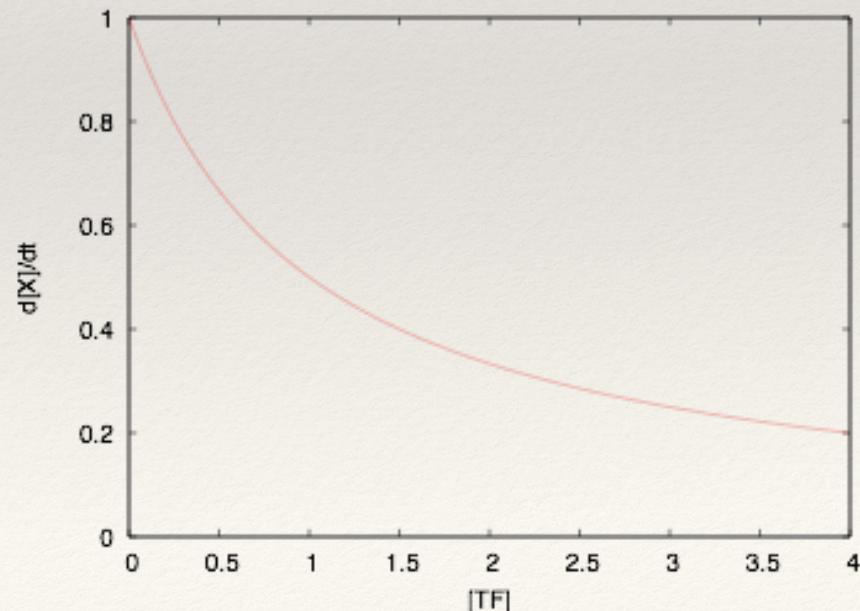
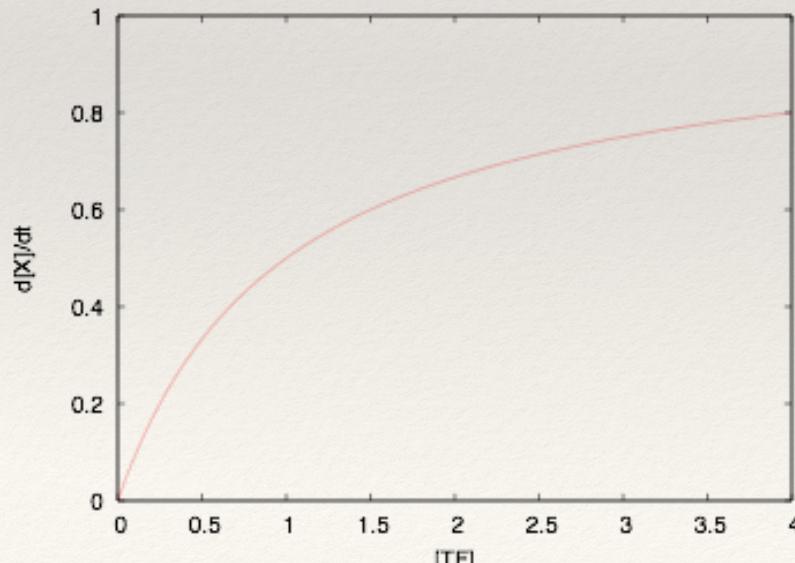
T is an activator

$$\frac{d[X]}{dt} = \frac{V_{\max} [T]}{K_A + [T]}$$



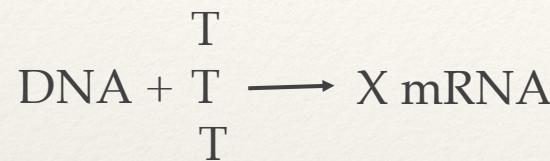
T is a repressor

$$\frac{d[X]}{dt} = \frac{V_{\max} K_A}{K_A + [T]}$$



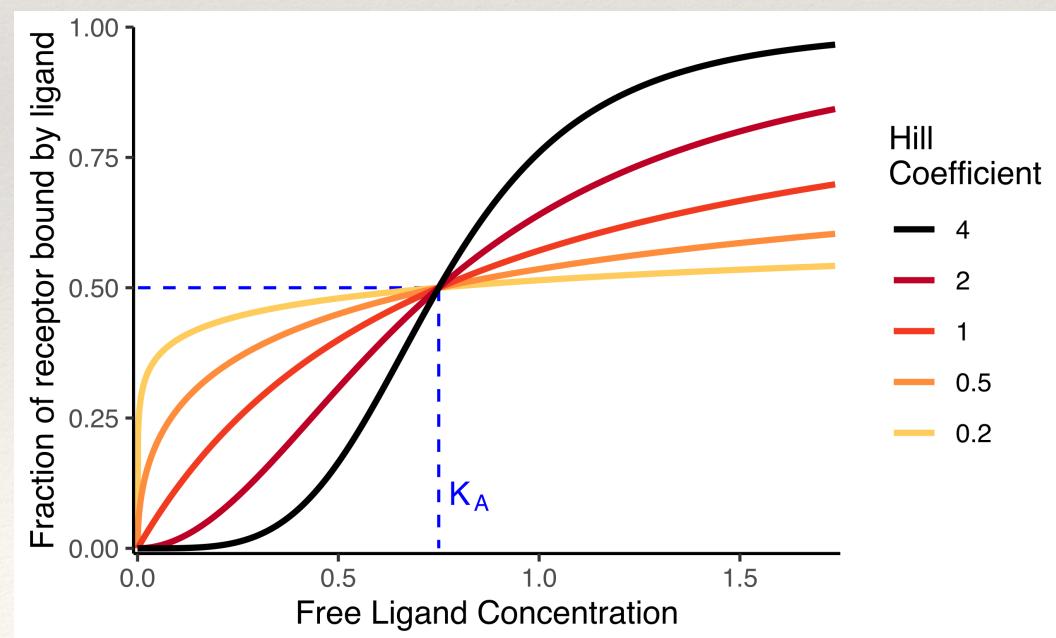
Hill Equation – Transcription

What if multiple factors are needed for transcription



T is an activator

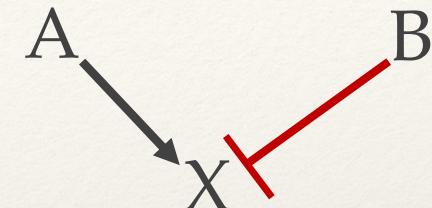
$$\frac{d[X]}{dt} = \frac{V_{\max} [T]^n}{K_A^n + [T]^n}$$



Hill Equation – Transcription

What if multiple factors of different types with different actions are needed for transcription:

$$\frac{d[X]}{dt} = \frac{V_{max} [A]^n}{K_1^n + [A]^n} + \frac{V_{max} K_2^n}{K_2^n + [B]^n}$$

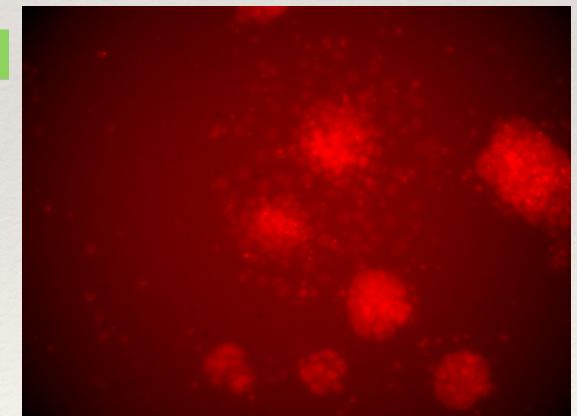
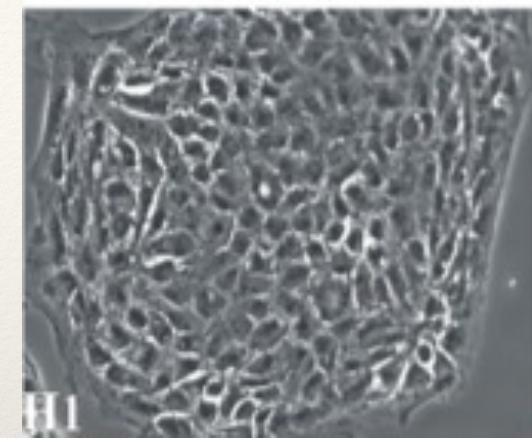
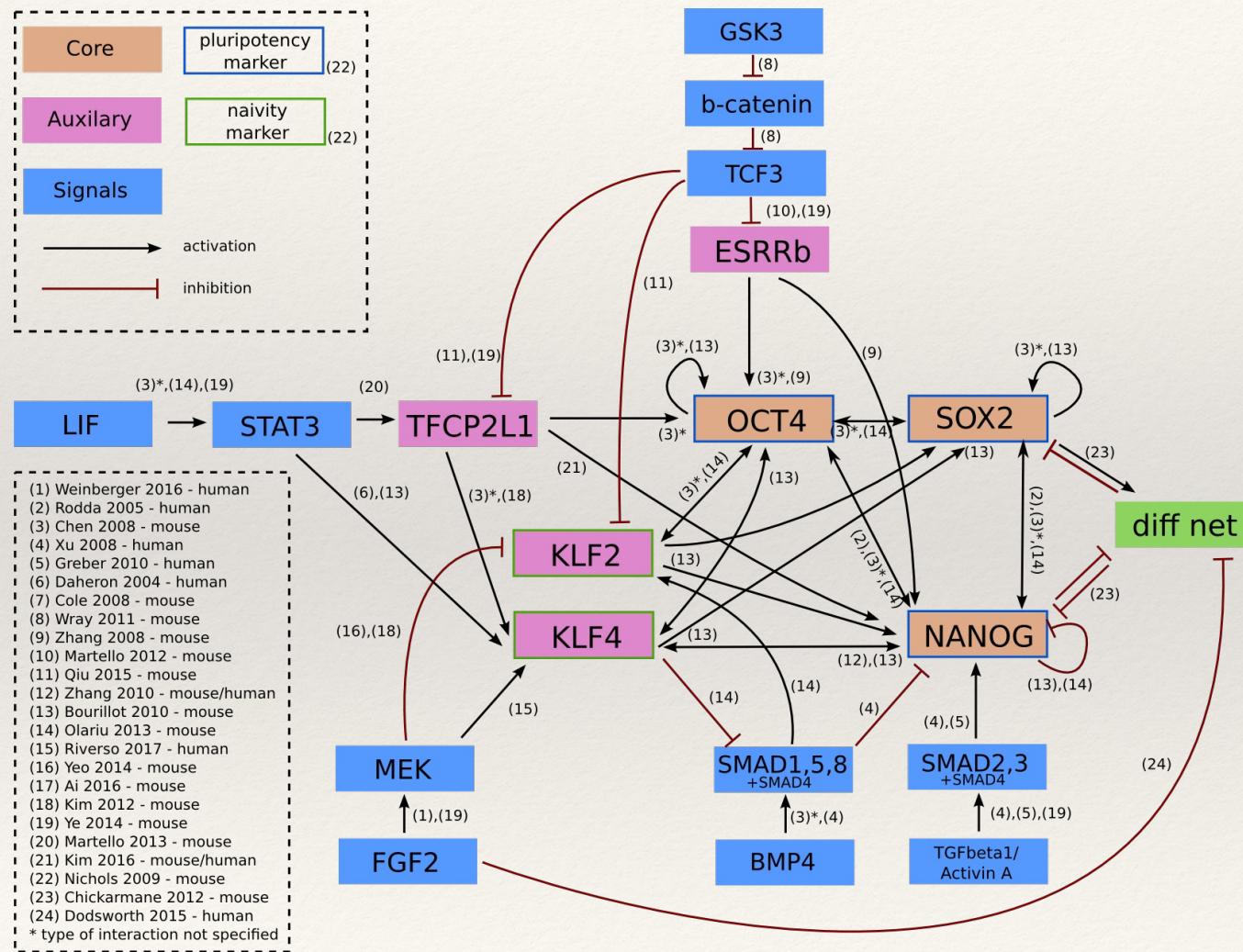


mRNA has a certain life span – therefore it dies proportional to a decay rate γ

Full model for the three node network

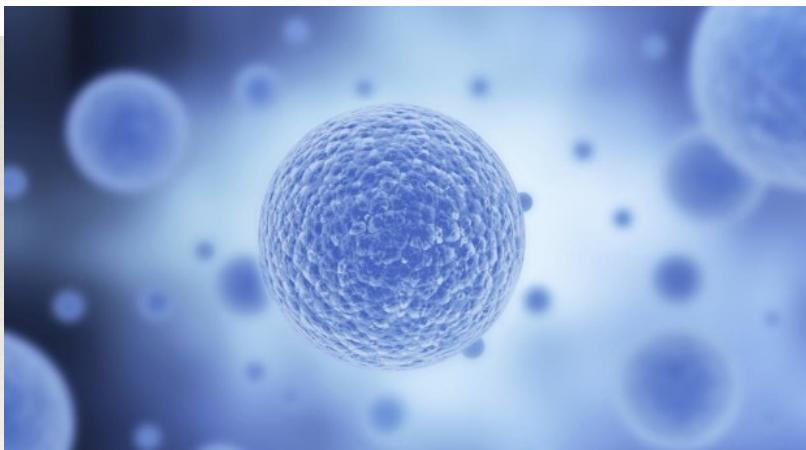
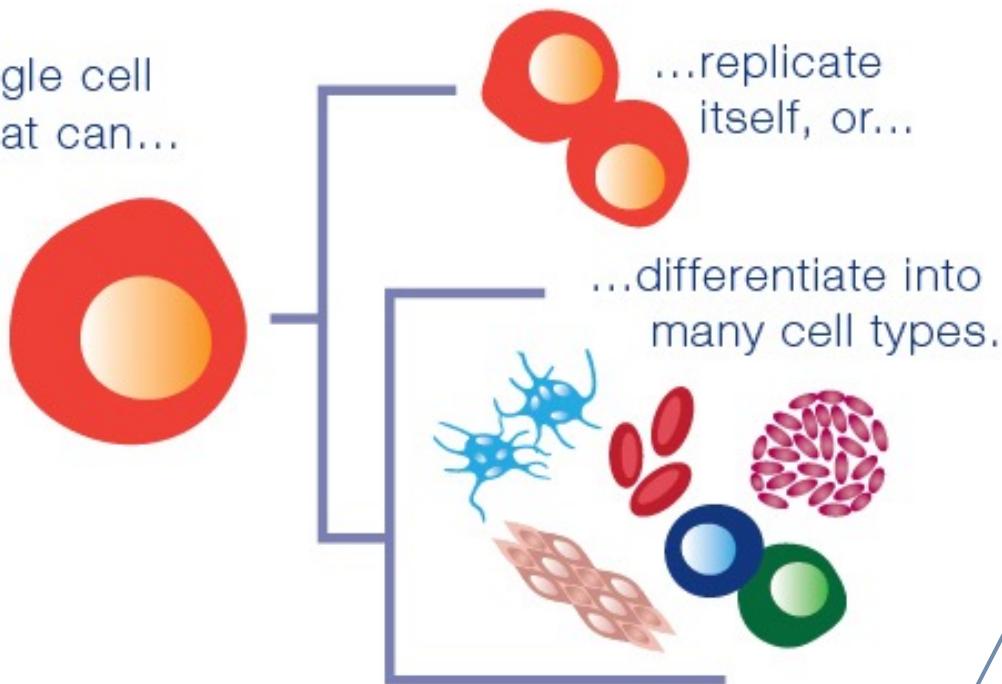
$$\frac{d[X]}{dt} = \frac{V_{max} [A]^n}{K_1^n + [A]^n} + \frac{V_{max} K_2^n}{K_2^n + [B]^n} - \gamma [X]$$

Gene Regulatory Network – Embryonic Stem Cells



What is a Stem Cell?

a single cell
that can...



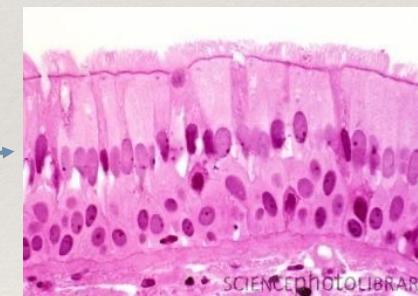
Images: nature.com



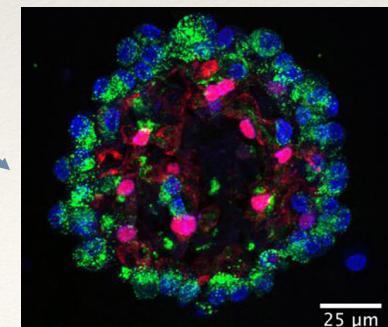
Blood



Neuron



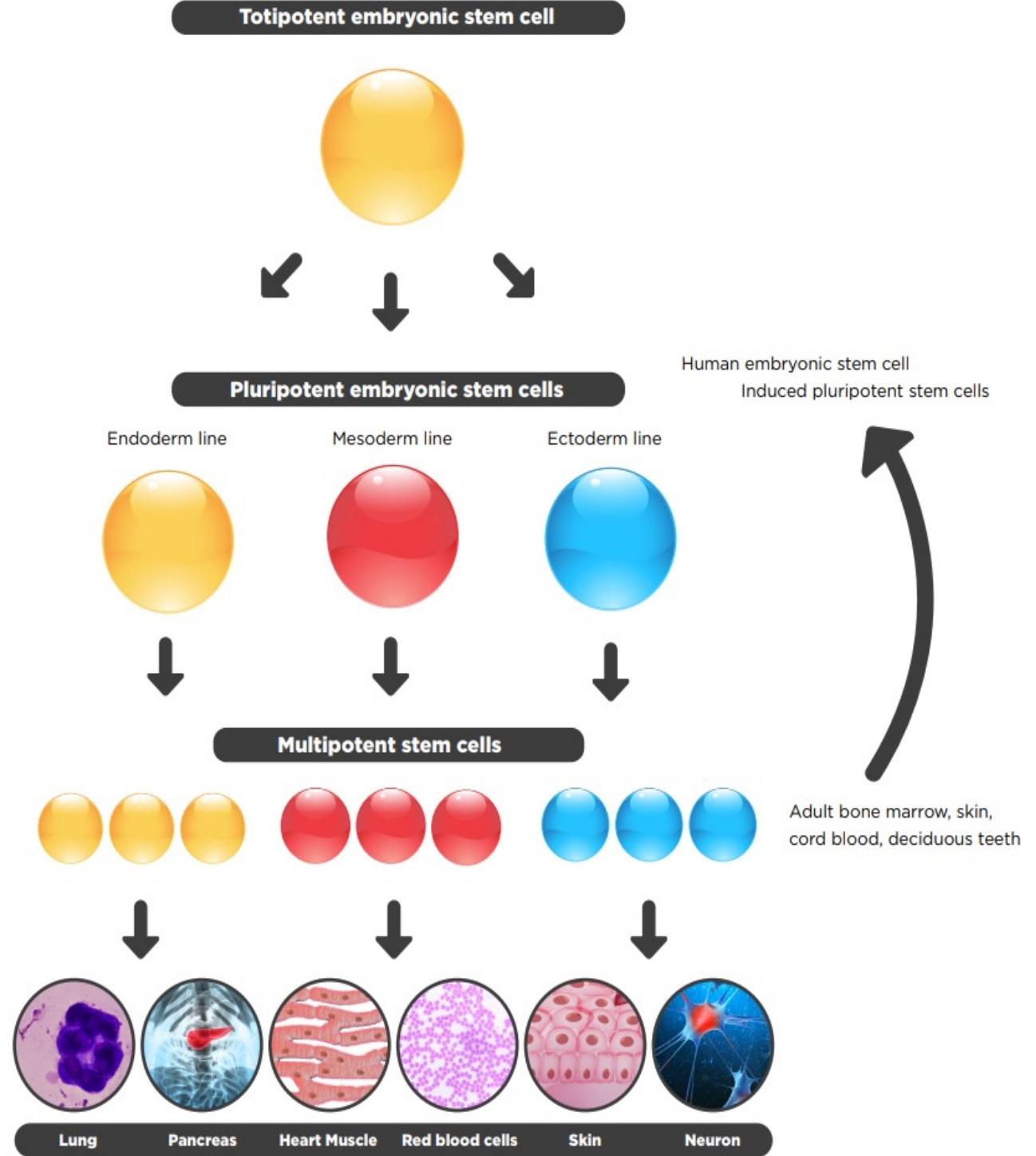
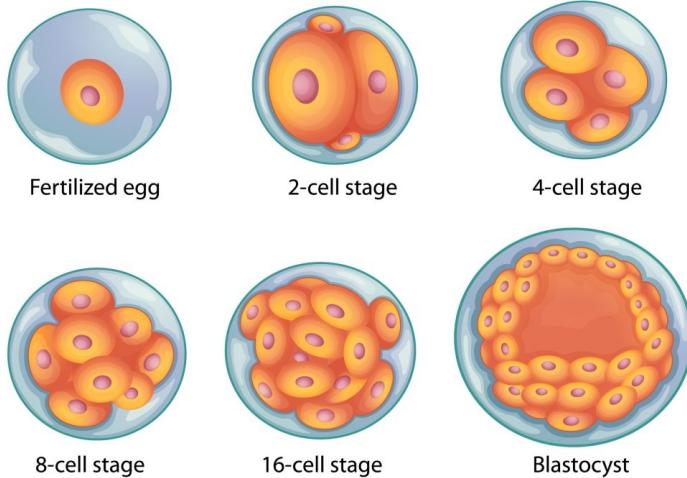
Skin



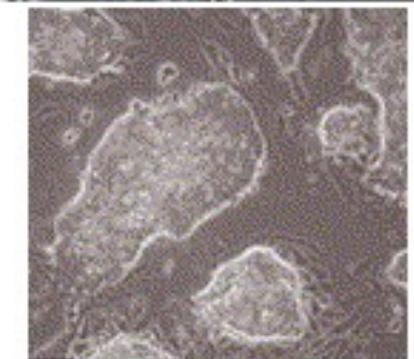
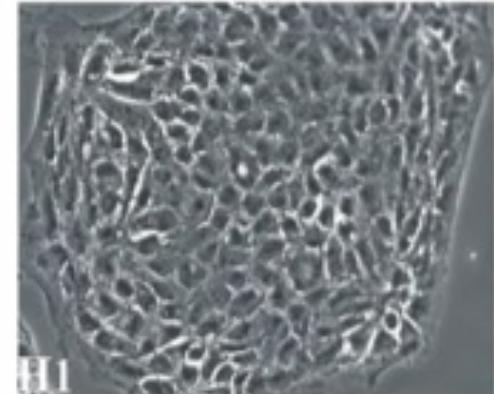
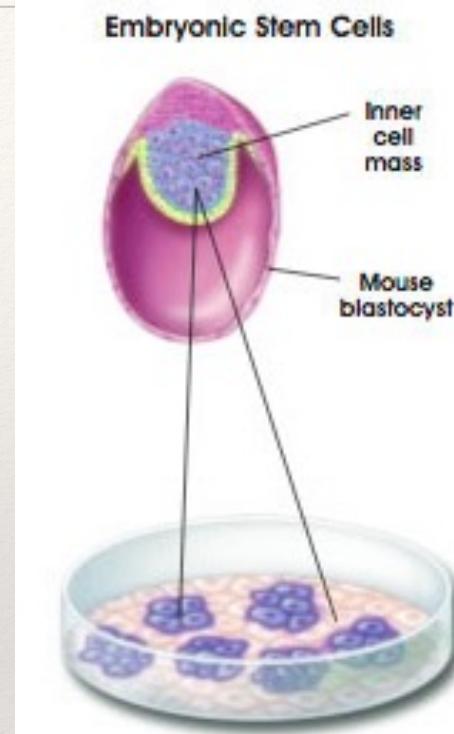
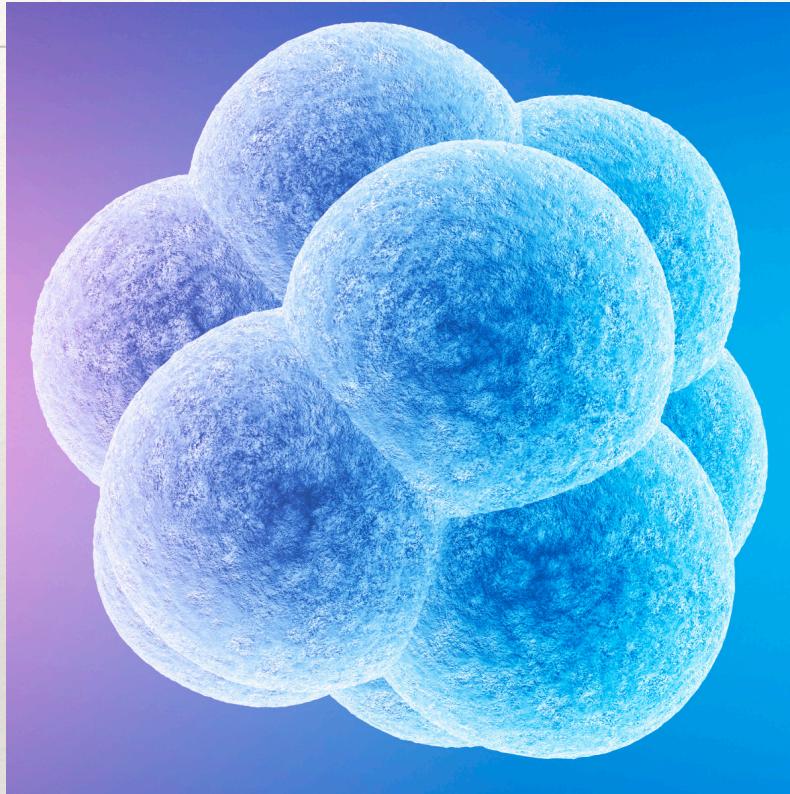
Lung

Cell Potency

Human Embryonic Development



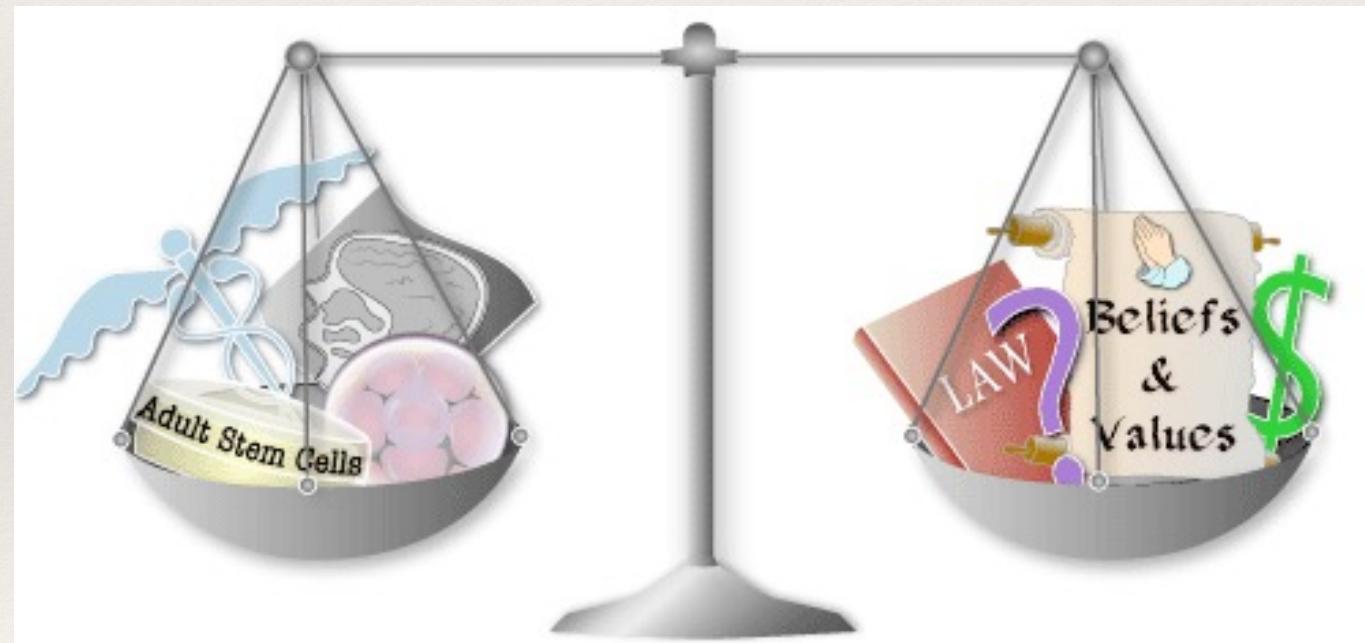
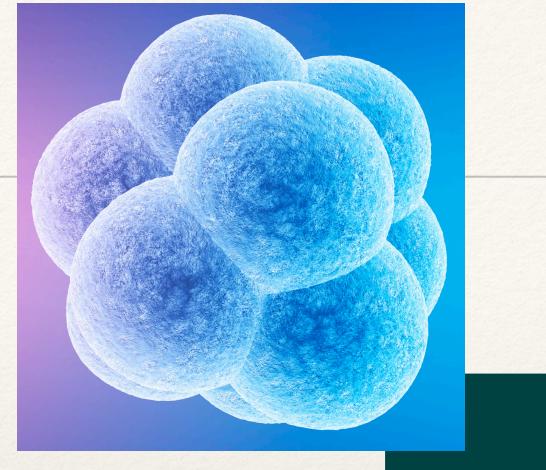
Embryonic Stem Cells



Mouse Embryonic Stem Cells 1981

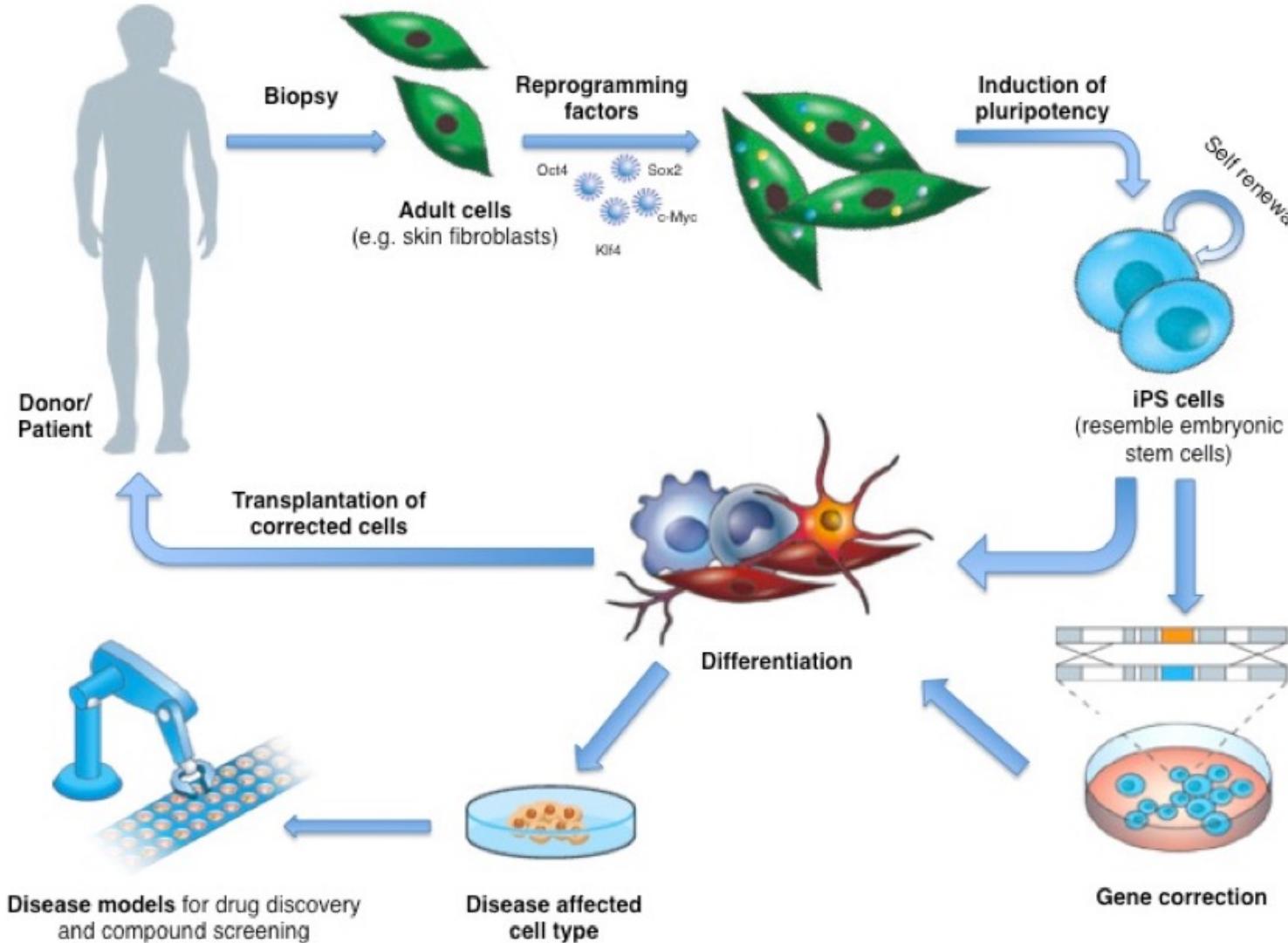
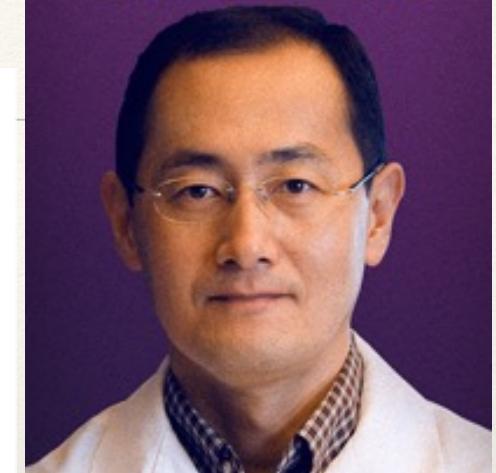
Human Embryonic Stem Cells 1998

Controversy



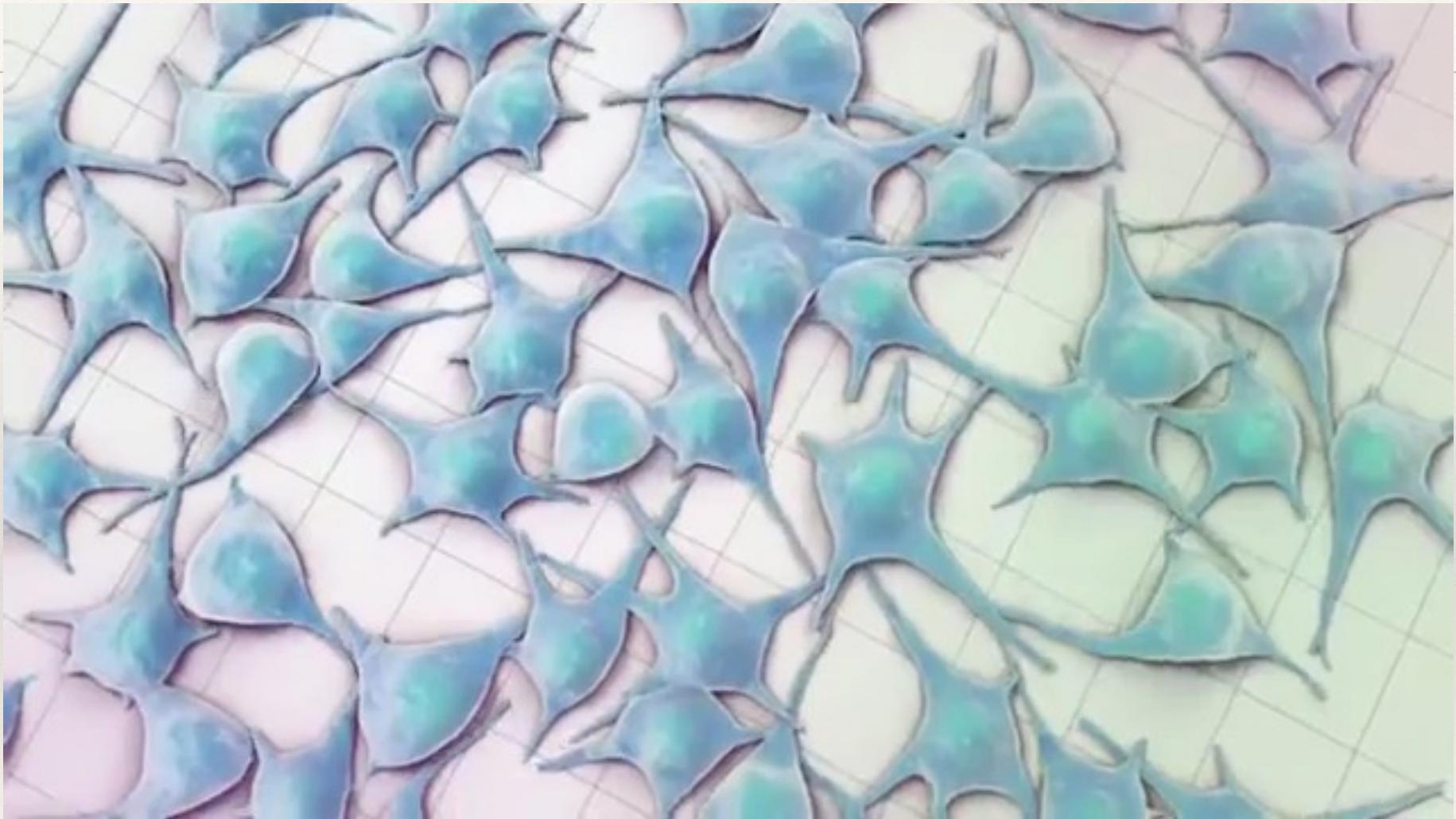
Cell Reprogramming

SHINYA YAMANAKA
2012 NOBEL PRIZE
IN MEDICINE



M. Rossbach

Movie Cell Reprogramming



Cell Reprogramming

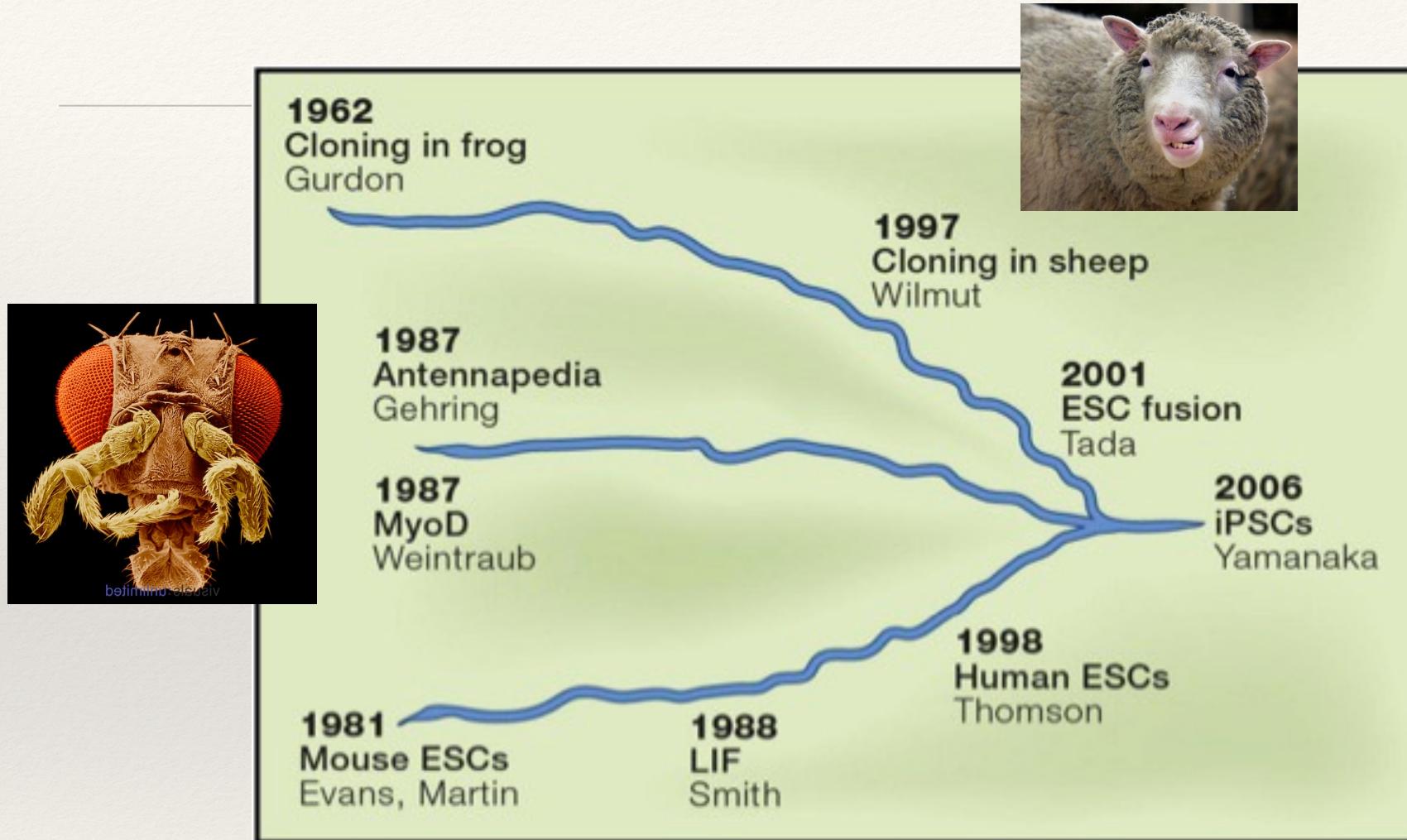


Image: Yamanaka 2011

Clinical trials for cell therapies

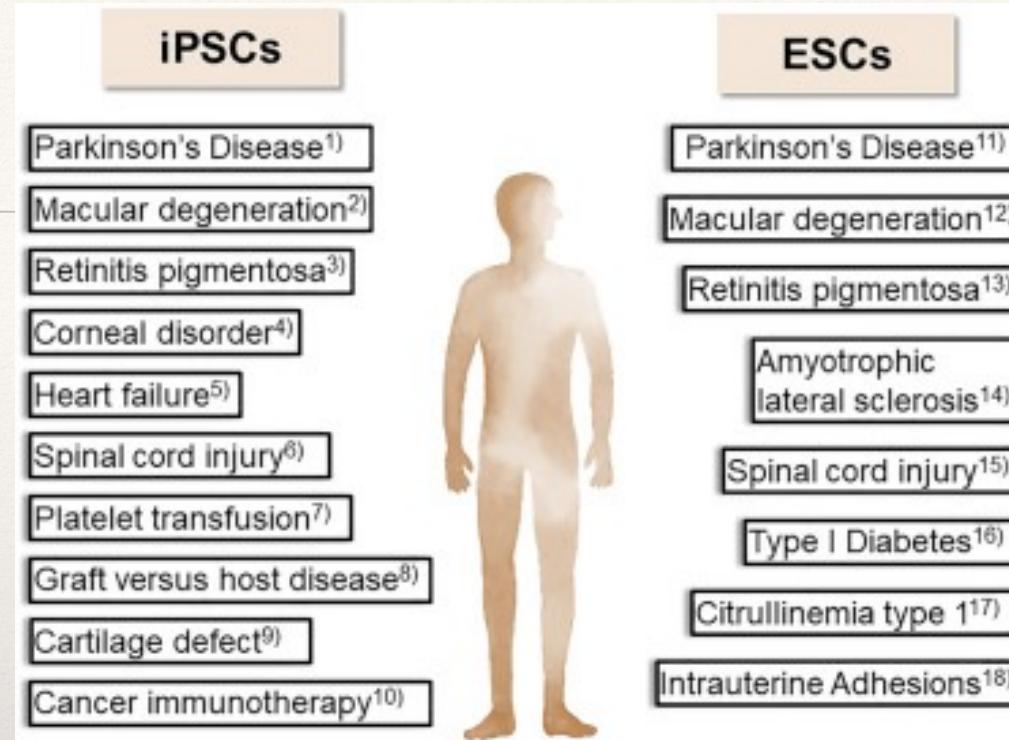


Image: Yamanka 2020

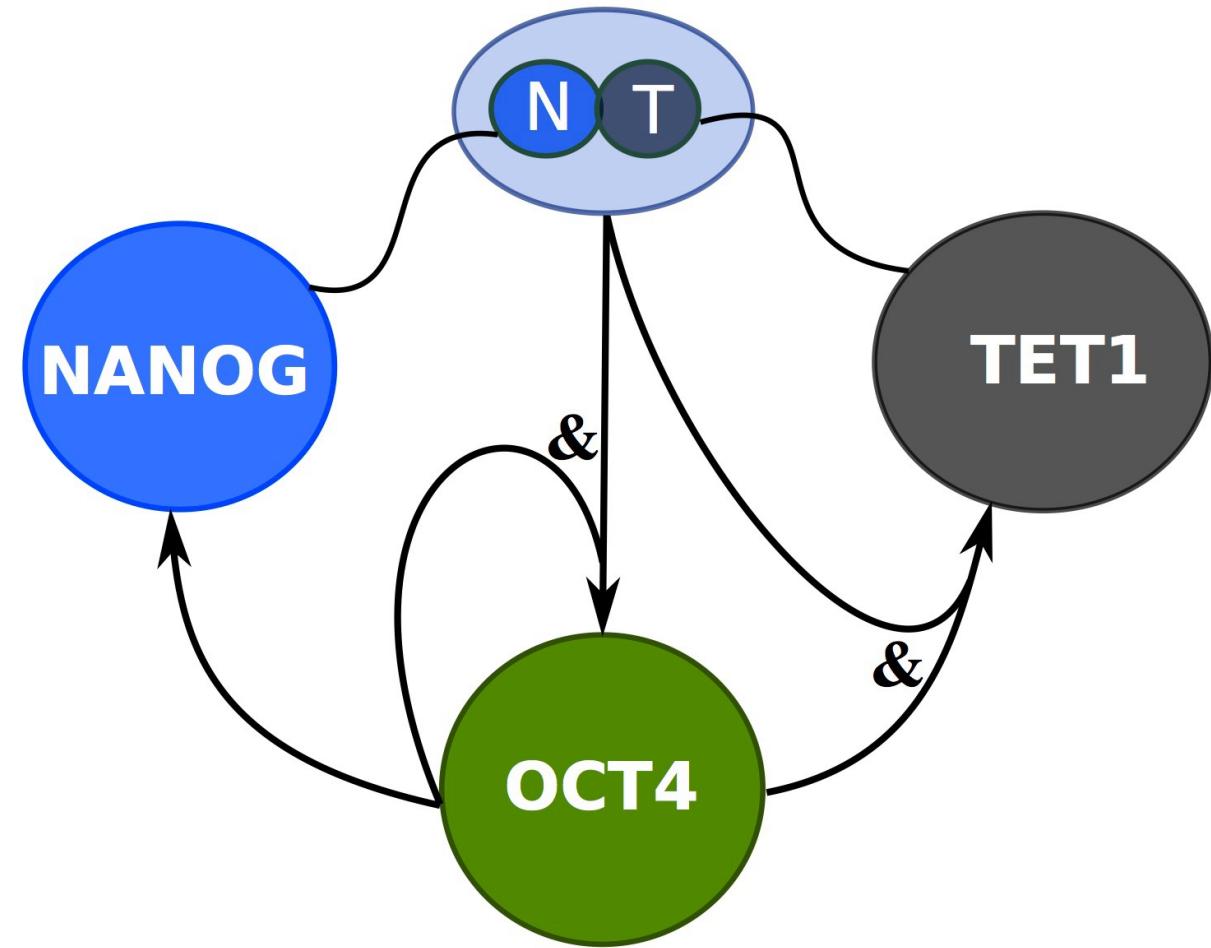
Challenges

- Low efficiency to produce the transplantable cells
 - Tumorigenicity
 - Immunogenicity
 - Heterogeneity

Possible Solutions

- Interdisciplinary studies – use systems biology to find reprogramming barriers
- Direct reprogramming
- Systems Biology identify the core mechanisms leading to heterogeneity

Simplified Gene Regulatory Network Topology



Olariu et al. (2016) Nanog, Oct4 and Tet1 interplay in establishing pluripotency.

Costa et al. Nature(2014), Koh et al. Cell Stem Cell(2011), Young R.A. Cell(2011)

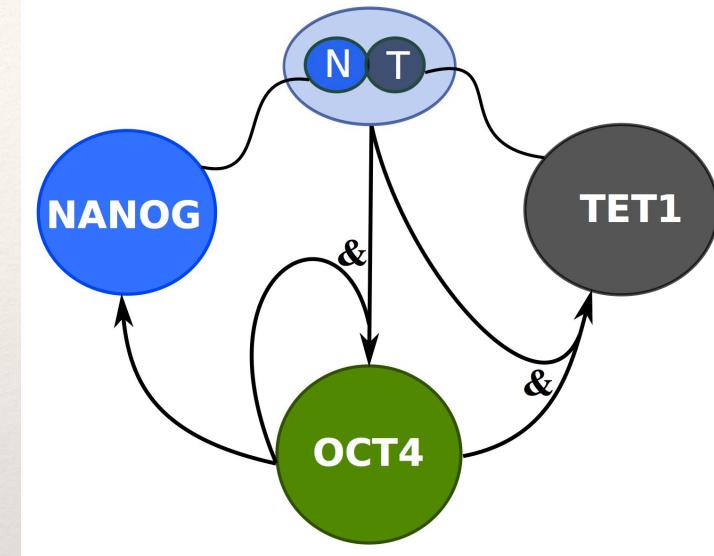
Fast Complex Formation

$$[N_{Free}] + [T_{Free}] \rightleftharpoons [N|T]$$

$$K_d = \frac{[N_{Free}][T_{Free}]}{[N|T]}$$

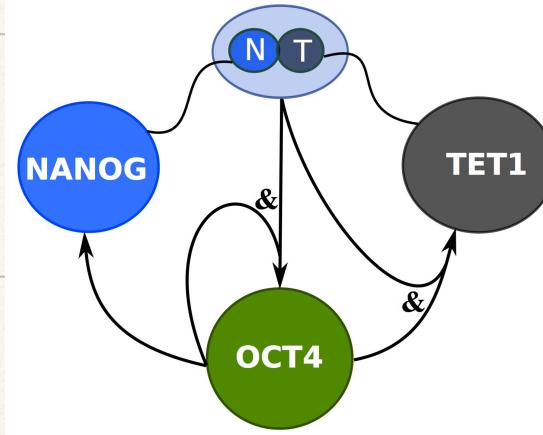
$$[N_{total}] = [N_{Free}] + [N|T]$$

$$[T_{total}] = [T_{Free}] + [N|T]$$



$$[N|T] = \frac{K_d + [N_{total}] + [T_{total}]}{2} - \sqrt{\left(\frac{K_d + [N_{total}] + [T_{total}]}{2}\right)^2 - [N_{total}] \cdot [T_{total}]}$$

Slow Gene Regulation

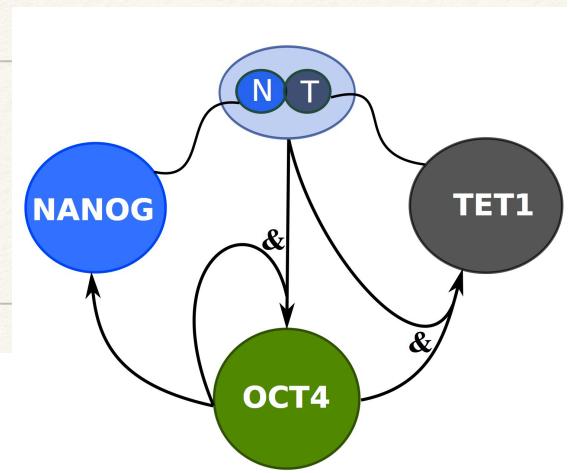
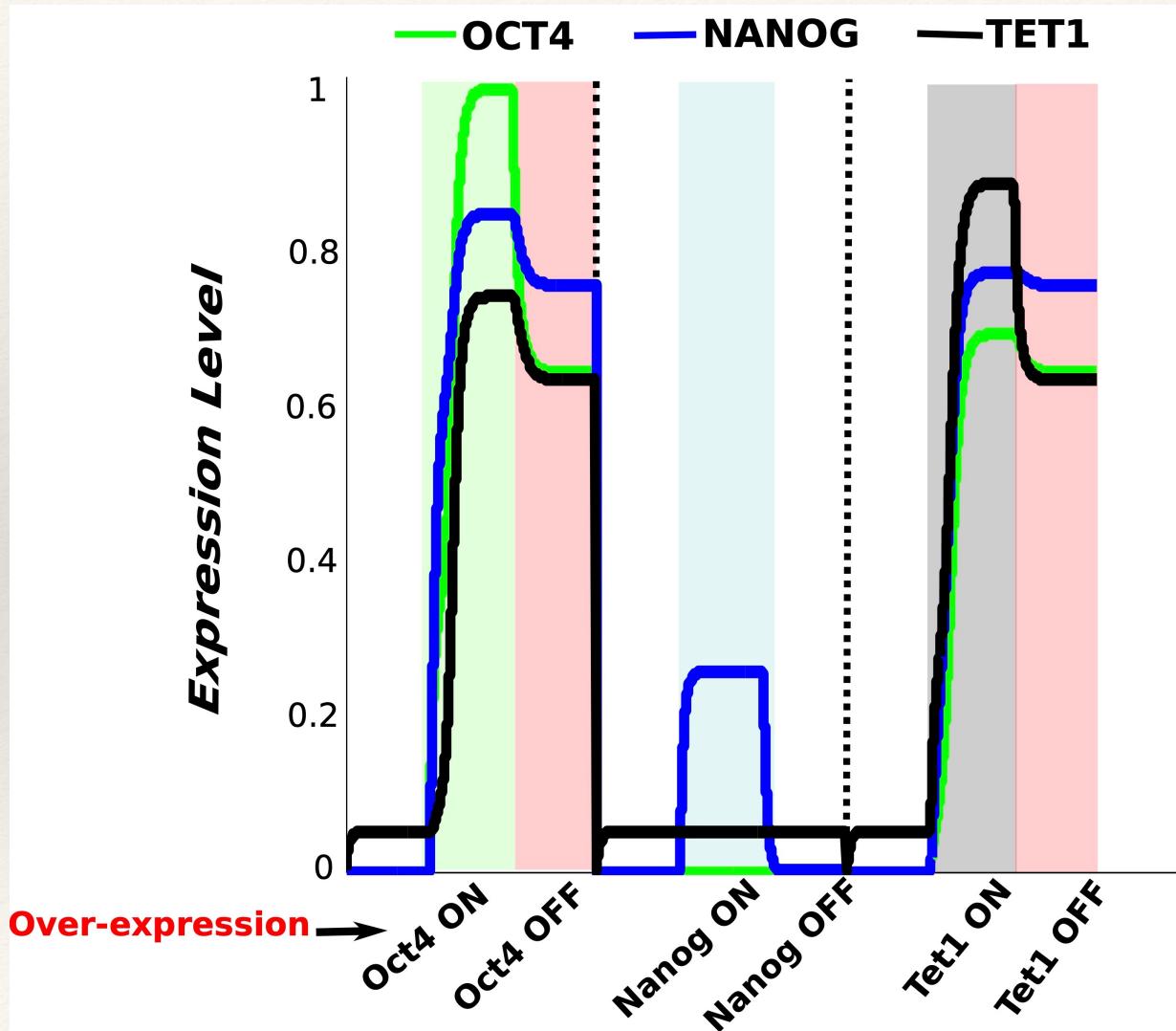


$$\frac{\partial [N_{Total}]}{\partial t} = N_{over} + LIF + p_N \cdot \frac{\frac{[O_{Total}]}{K_O}}{1 + \frac{[O_{Total}]}{K_O}} - [N_{Total}]$$

$$\frac{\partial [O_{Total}]}{\partial t} = O_{over} + LIF + p_O \cdot \frac{\left(\frac{[N|T]}{K_{NT}}\right)^n \cdot \frac{[O_{Total}]}{K_O}}{1 + \left(\frac{[N|T]}{K_{NT}}\right)^n \cdot \frac{[O_{Total}]}{K_O}} - [O_{Total}]$$

$$\frac{\partial [T_{Total}]}{\partial t} = T_{over} + p_T \cdot \frac{\left(\frac{[N|T]}{K_{NT}}\right)^n \cdot \frac{[O_{Total}]}{K_O}}{1 + \left(\frac{[N|T]}{K_{NT}}\right)^n \cdot \frac{[O_{Total}]}{K_O}} - [T_{Total}]$$

Reprogramming Simulation Results



Cell Reprogramming Project

- Implement the deterministic model for cell reprogramming.
- Pay attention at the fast protein complex formation.
- Reproduce the results on the previous slide.
- Take the parameters values and models details from the publication - Olariu et al. 2016 Nanog, Oct4 and Tet1 interplay in establishing pluripotency. *Sci Rep* 6, 25438

Please note that LIF is ON only if the cell is in a pluripotent state.
If for example, Nanog over-expression does not push the cells in a pluripotent state then one cannot have LIF active for this scenario.