Modelling and Analysis in Bioinformatics: Simulating dynamical network models

Antti Honkela

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Local overview of the course

- Past two weeks: abstract networks
- Upcoming two weeks: simulating dynamical network models and network inference
  - This week: How to simulate models of interacting entities?
  - Next week: How to infer unknown networks from observations?

This ain't no physics

- Biology does not follow universal laws.

> *"Nothing in Biology Makes Sense Except in the Light of Evolution"*
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> —Theodosius Dobzhansky

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- We study biology through models, which are simplifications of the world.

  > *"Essentially, all models are wrong, but some are useful."*
  >
  > —George E. P. Box

Gene regulation?

What is gene regulation?

Why are genes regulated?

How are genes regulated?

How can gene regulation be modelled?

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Why are genes regulated?

How are genes regulated?

How can gene regulation be modelled?

Learning goals for this week

- To understand the *reasons for the complexity* of gene regulation.
- To know *modelling formalisms* used to model gene regulation.
- To be able to *simulate* gene expression and regulation.
- To understand the effects of system parameters through simulation.

Outline

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Gene expression

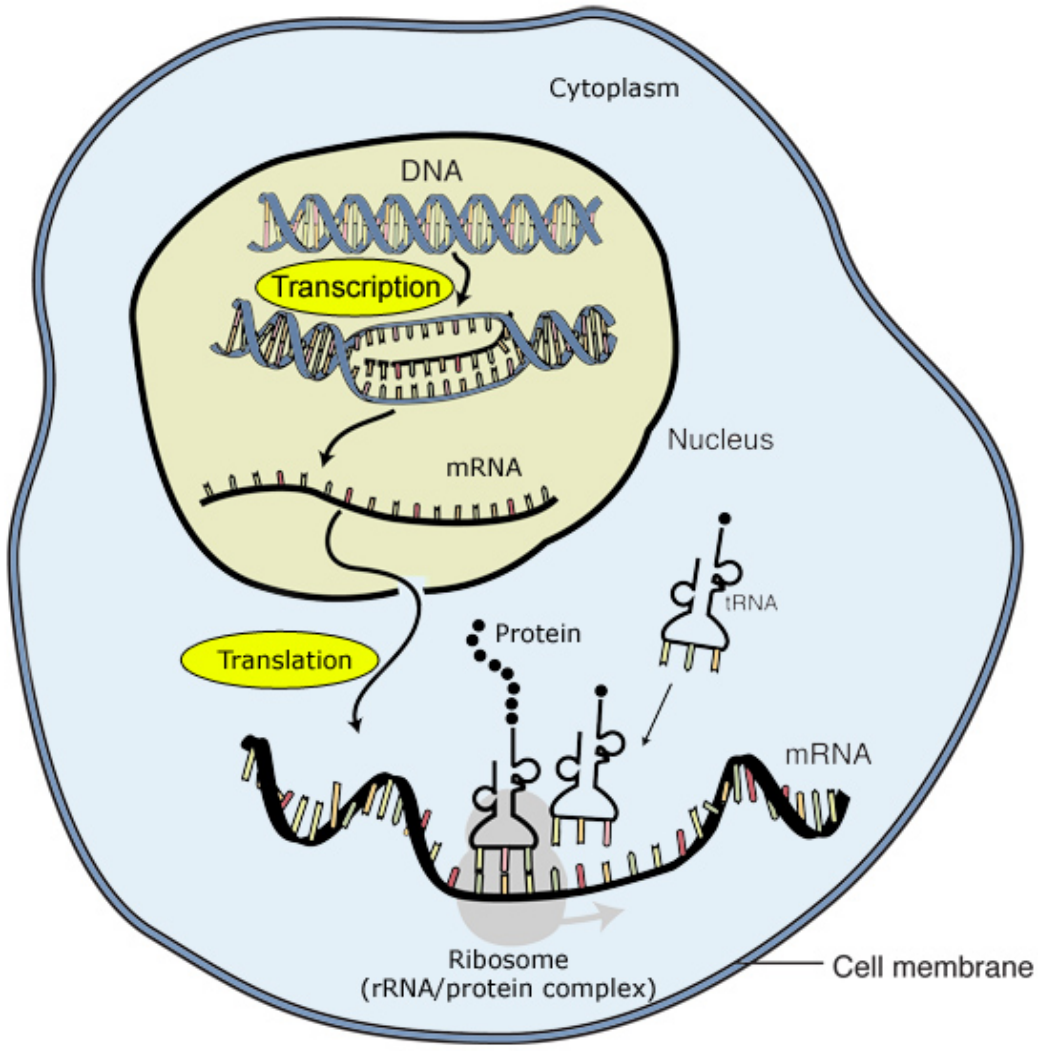
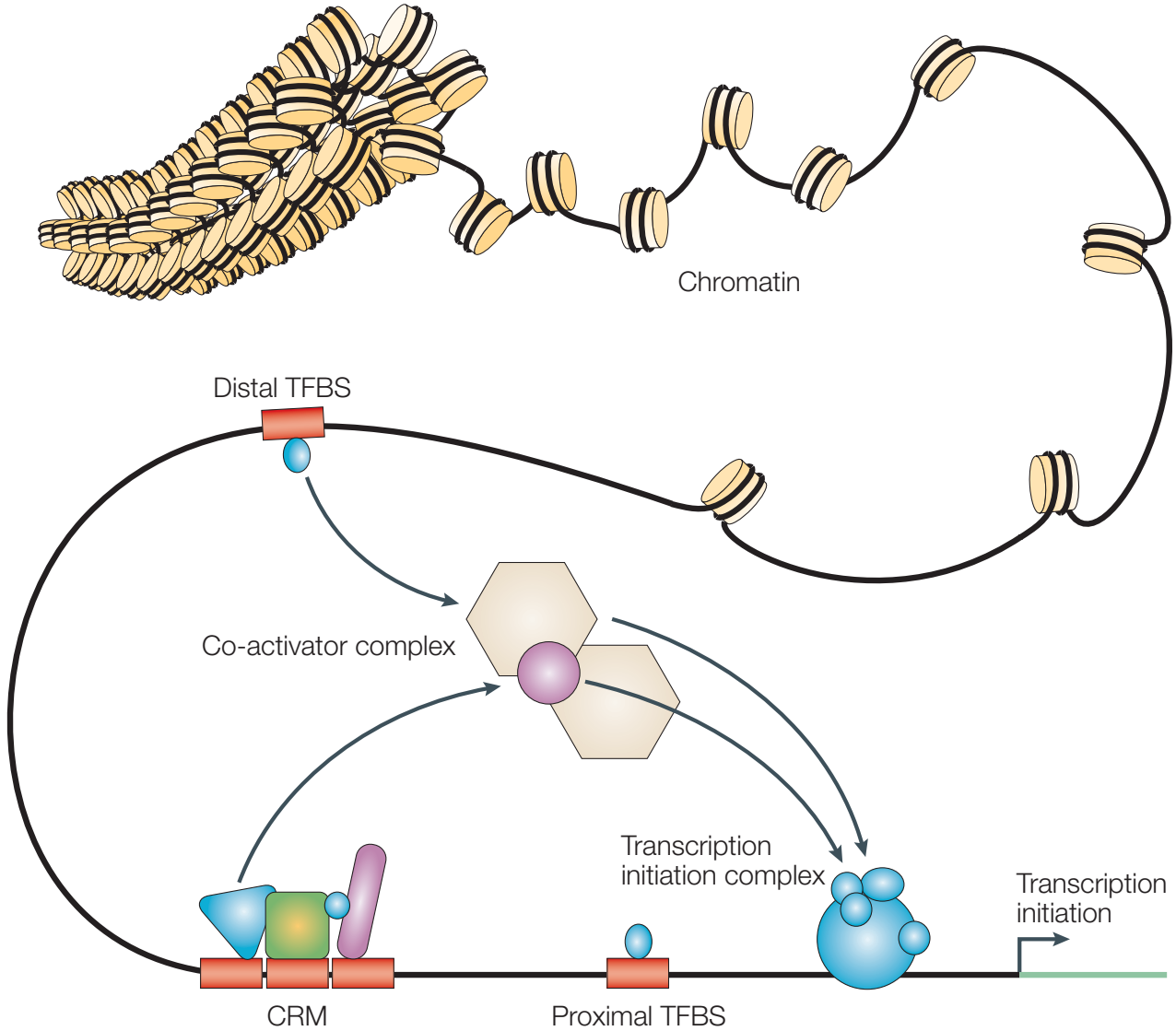


Image adapted from: National Human Genome Research Institute.

Transcrption regulation



(Image from: Wasserman & Sandelin. *Nat Rev Genet.* 5(4):276-87, 2004.)

Facts about gene regulation

- ≈20,000 genes in human, estimated 2000 of those are transcription factors (TFs)
- 250,000+ proteins
- Gene expression is highly spatially and temporally regulated
- E.g. nearly half of mouse genes vary by circadian rhythm somewhere in the body

The process and regulation of gene expression I

1. Recruitment and formation of transcription initiation complex
   - DNA accessibility, TF binding, epigenetics

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   - Pausing, polymerase falling off
4. Transcription termination
   - Termination factors

The process and regulation of gene expression II

5. Splicing and other RNA processing
    - Splicing factors

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The process and regulation of gene expression II

5. Splicing and other RNA processing
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6. mRNA transport
   - Various RNA-binding proteins
7. Translation
   - Ribosome function, tRNA availability
8. mRNA degradation
   - Various mechanisms; incl. micro RNAs (miRNAs) and nonsense-mediated mRNA decay

Example: regulation of development

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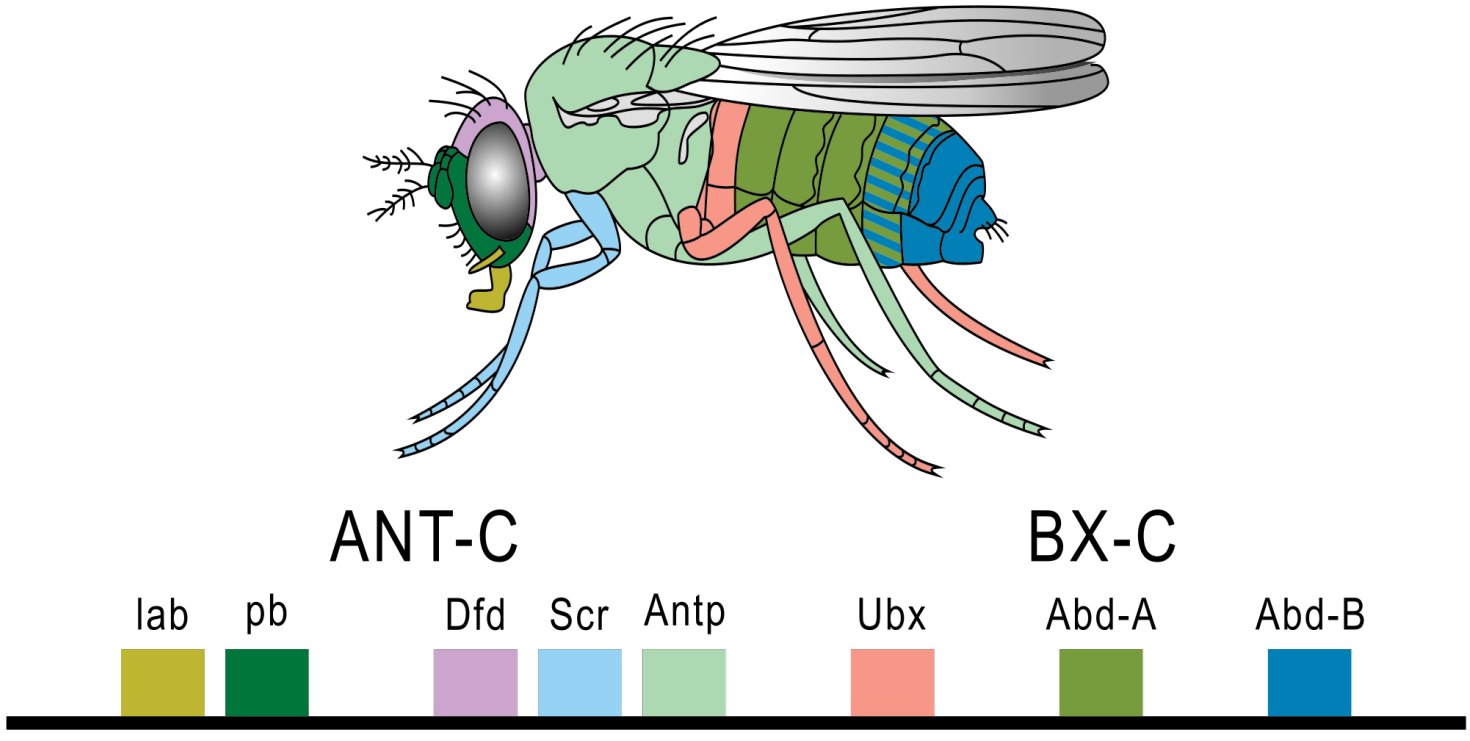

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A cell as a dynamical system

The state of the cell as a d-dimensional vector:

$$\mathbf{x}(t) = (x_1(t), \ldots, x_d(t))^T \in \mathcal{C} \subset \mathbb{R}^d$$

Questions:

- Which variables should the state include?
- What values are allowed for the variables?
- How to model the evolution of the state over time?
- What about spatial aspects? (Ignored here)

Different approaches for simulating a cell

Discrete state – Continuous state

Discrete time – Continuous time

Deterministic – Stochastic

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An example system

Consider a system with two regulators (transcription factors) ANT and BEE regulating a target gene TAR:

$$\mathbf{x}(t) = \begin{pmatrix} x_{ANT}(t) \\ x_{BEE}(t) \\ x_{TAR}(t) \end{pmatrix}$$

Ordinary differential equations: Modelling a deterministic continuous time / continuous state process

A general form for a differential equation:

$$\frac{d\mathbf{x}(t)}{dt} = f(\mathbf{x}(t), t)$$

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Example of a regulatory model

$$f(\mathbf{x}(t), t) = f(\mathbf{x}(t)) = \begin{pmatrix} -\lambda_{ANT} x_{ANT}(t) \\ -\lambda_{BEE} x_{BEE}(t) \\ c \cdot x_{ANT}(t) x_{BEE}(t) - \lambda_{TAR} x_{TAR}(t) \end{pmatrix}$$

Simulating ordinary differential equations (ODEs)

Consider an *initial value problem*

$$\frac{d\mathbf{x}(t)}{dt} = f(\mathbf{x}(t), t), \quad \mathbf{x}(0) = \mathbf{x}_0$$

Numerical solution in theory (Euler's method):

- Pick a (small) time step δ
- Simulate a single discrete step:

$$\mathbf{x}(t + \delta) = \mathbf{x}(t) + \delta \cdot f(\mathbf{x}(t), t)$$

In practice:

- Use a ready ODE solver

Ordinary differential equation models in practice

Pros:

Cons:

Ordinary differential equation models in practice

Pros:

- Powerful framework
- Can define mechanistic models with interpretable parameters
- Efficient solvers widely available

Cons:

- Cannot model discrete variables and discrete transitions
- Deterministic model can be unrealistic

Modelling a stochastic continuous time / continuous state process

A general form for a stochastic differential equation:

$$d\mathbf{x}(t) = f(\mathbf{x}(t), t)dt + \Sigma(\mathbf{x}(t), t)dB(t)$$

where $dB(t)$ is a differential Brownian motion satisfying in a suitable sense (Itô integral)

$$\int_0^t dB(t) = N(0, t) \quad (cf. \int_0^t dt = t)$$

Simulating a stochastic continuous time / continuous state process

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Numerical solution in theory (Euler-Maruyama method):

- Pick a (small) time step δ
- Simulate a single discrete step:

$$\mathbf{x}(t + \delta) = \mathbf{x}(t) + \delta \cdot f(\mathbf{x}(t), t) + \Sigma(\mathbf{x}(t), t)\eta_t,$$

where

$$\eta_t \sim N(0, \delta\mathbf{I})$$

Stochastic differential equation models in practice

Pros:

Cons:

Stochastic differential equation models in practice

Pros:

- Powerful framework
- Can define mechanistic models with interpretable parameters
- Can provide very realistic stochastic models of continuous phenomena

Cons:

- Cannot model discrete variables and discrete transitions
- Solvers not as widely available as ODE solvers

Discrete states and Markov property

- Some properties are inherently discrete (e.g. number of molecules x in a single cell)
- Can have a big impact on modelling small non-negative values
- For discrete states and jumps, duration of a state becomes important
- Common simplification: Markov property

$$p(\mathbf{x}(t+\delta)|\mathbf{x}(\tau \leq t)) = p(\mathbf{x}(t+\delta)|\mathbf{x}(t))$$

Markov jump processes: Modelling a stochastic continuous time / discrete state process

$$p(\mathbf{x}(t+dt)|\mathbf{x}(t)) = f(\mathbf{x}(t)), \quad \mathbf{x}(0) = \mathbf{x}_0$$

Simulation loop:

- Simulate the time until next change (depends on f)
- Simulate the change itself

Try it out in practice in the exercises!

Markov jump processes in practice

Pros:

Cons:

Markov jump processes in practice

Pros:

- Powerful framework
- Can define mechanistic models with interpretable parameters
- Can provide very realistic stochastic models of discrete phenomena

Cons:

- General purpose solves usually not available (but not too difficult to implement)
- Simulation can be really slow if many potential states

How to select the function f?

- Selecting f is a big modelling choice along with selecting the approach
- Assuming a well-mixed system of discrete entities one can derive an f for Markov jump process
- The average of this process follows a known ODE
- Stochasticity can be captured better by a SDE
- More about these in the study circle and the exercises

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Next steps

Thursday:

- Study circle on simulation methods
- Computer exercises on simulation methods

Next week:

- Network inference

Tasks for the study circle on Thursday

Papers:

- Gillespie D. Exact stochastic simulation of coupled chemical reactions. *Journal of physical chemistry* 81(25):2340–2361, 1977.
- Gillespie D. The chemical Langevin equation. *The journal of chemical physics* 113(1):297–306, 2000.

Tasks for different groups:

Tasks for the study circle on Thursday

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- Gillespie D. The chemical Langevin equation. *The journal of chemical physics* 113(1):297–306, 2000.

Tasks for different groups:

Group 1 (Last name starts with A-H)	Read Gillespie (1977) (especially Secs. I, IIIB, IIIC)
Group 2 (Last name starts with I-L)	Read Gillespie (2000) (especially Secs. I, II, III)
Group 3 (Last name starts with M-Z)	Read Gillespie (2000) (especially Secs. I, II, IV)