

The fundamentals of whole-cell modelling

Stochastic simulation in Julia

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December 2, 2024

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Whole-cell models for biological discovery

Minimal bacterium

Bacillus subtilis



Fundamental science

cell cycle, signal processing,
cell fate decision making

Model bacterium

Escherichia coli

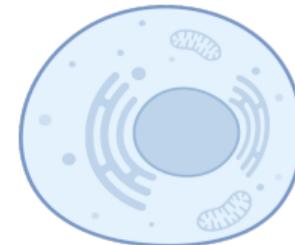


Bioengineering + synthetic biology

biosensors, bioproduction,
fermentation

Archetypal human cell

Homo sapiens H1-hESC

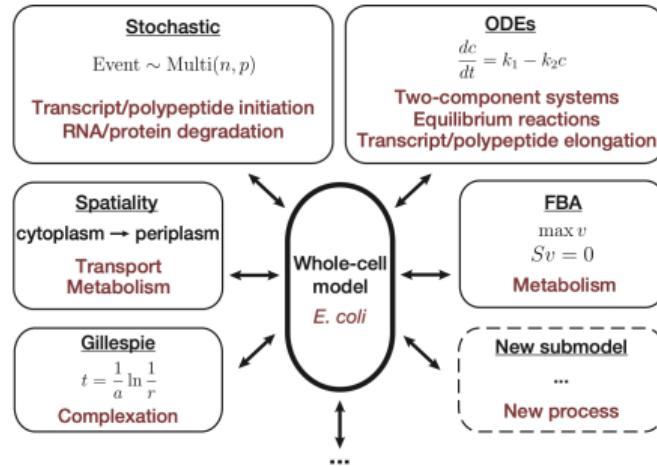


Medicine

digital twins, personalised
and precision therapy

The whole-cell modelling project (Covert lab)

Interpretability vs predictive power: mechanistic (biologically interpretable) vs models that can capture behaviour at the genome scale (usually “black box” ML models)



Sun et al, *EcoSal Plus*, 2019

Modular approach: whole-cell modelling can integrate different types of models to meet the scale of an entire organism **while including mechanistic interactions**

Stochastic vs deterministic modelling

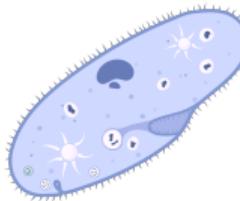
Many aspects of the behaviours of biological systems can be understood simply in terms of the dynamics of the averaged state variables and their **deterministic evolution equations**

Stochastic vs deterministic modelling

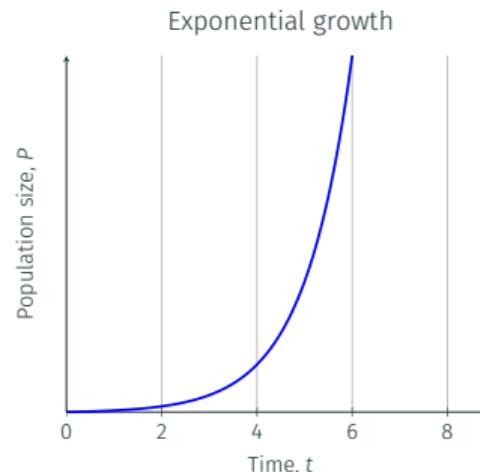
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Population modelling 101

$$\frac{dP}{dt} = kP$$



Paramecium



Stochastic vs deterministic modelling

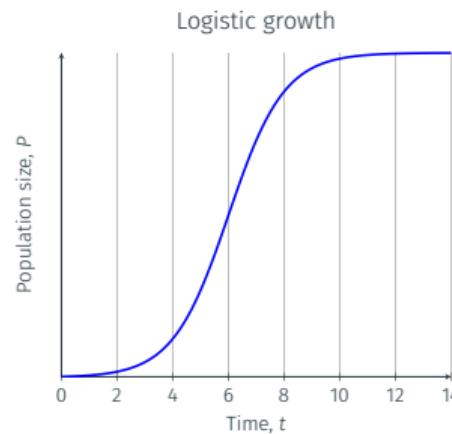
Many aspects of the behaviours of biological systems can be understood simply in terms of the dynamics of the averaged state variables and their **deterministic evolution equations**

Population modelling 102

$$\frac{dP}{dt} = kP(M - P)$$



Fur seal



Stochastic vs deterministic modelling

Many aspects of the behaviours of biological systems can be understood simply in terms of the dynamics of the averaged state variables and their **deterministic evolution equations**

Population modelling 102

$$\frac{dP}{dt} = kP(M - P)$$

Since such systems typically involve **very large numbers** of ensemble members, fluctuations are highly suppressed with respect to the mean behaviour.

Stochastic vs deterministic modelling

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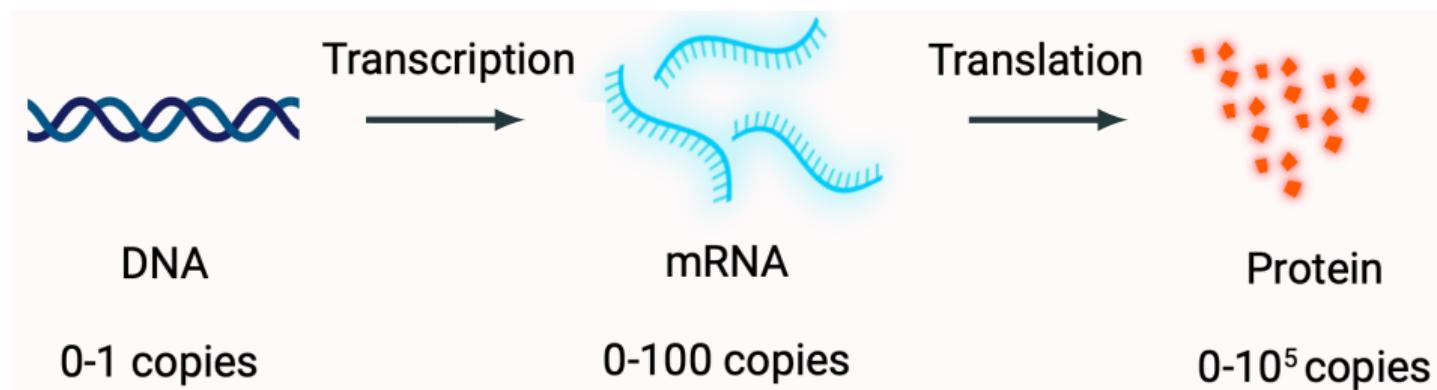
Population modelling 102

$$\frac{dP}{dt} = kP(M - P)$$

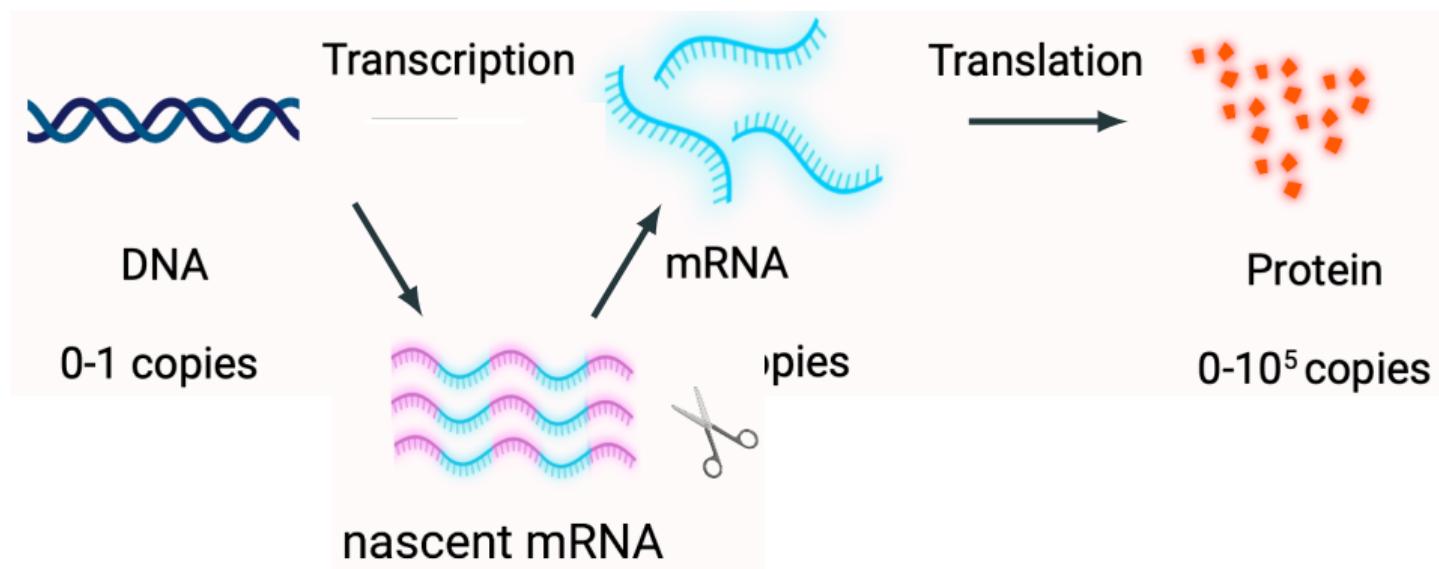
Since such systems typically involve **very large numbers** of ensemble members, fluctuations are highly suppressed with respect to the mean behaviour.

Central dogma of molecular biology

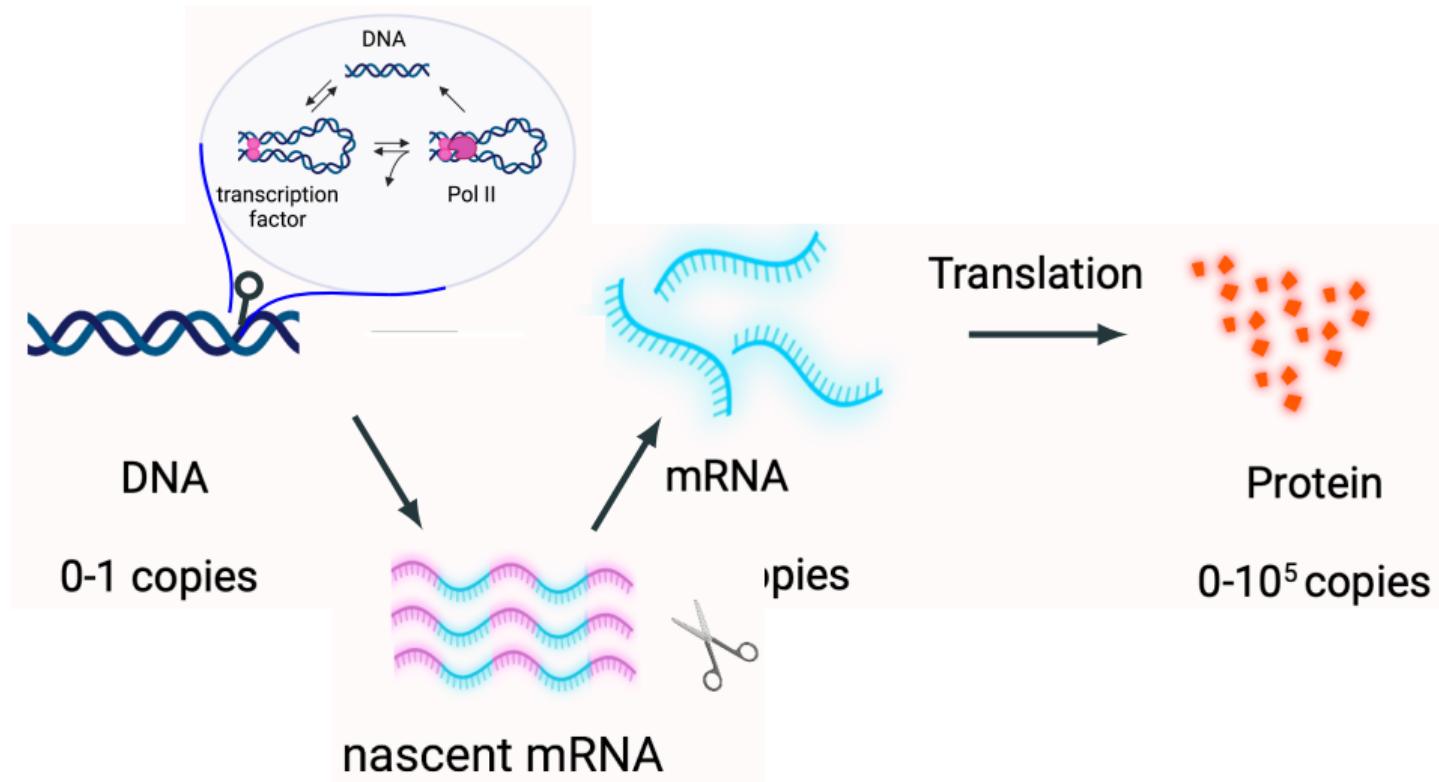
In low intracellular copy number regimes noise becomes important....and deterministic models are not able to capture the system's behaviour



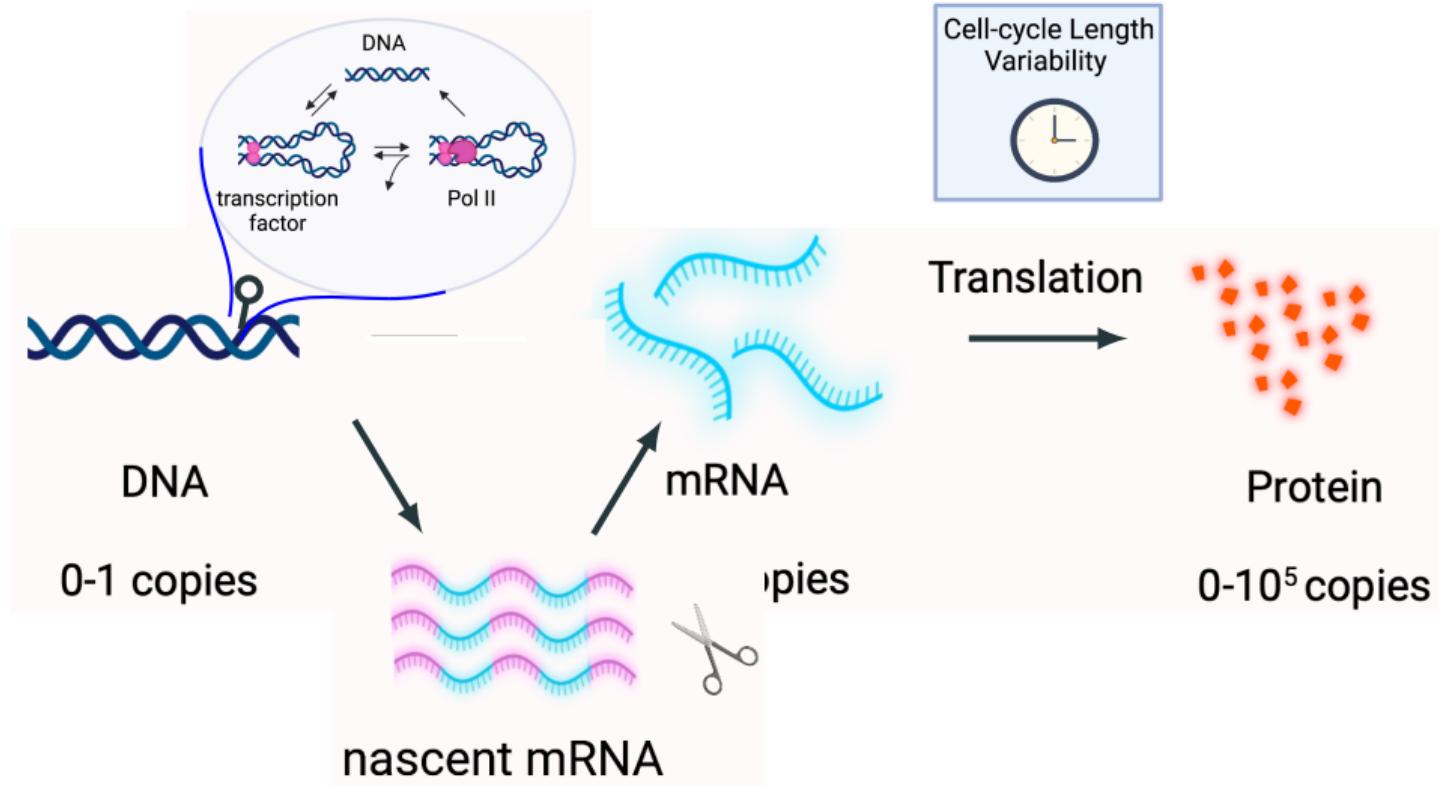
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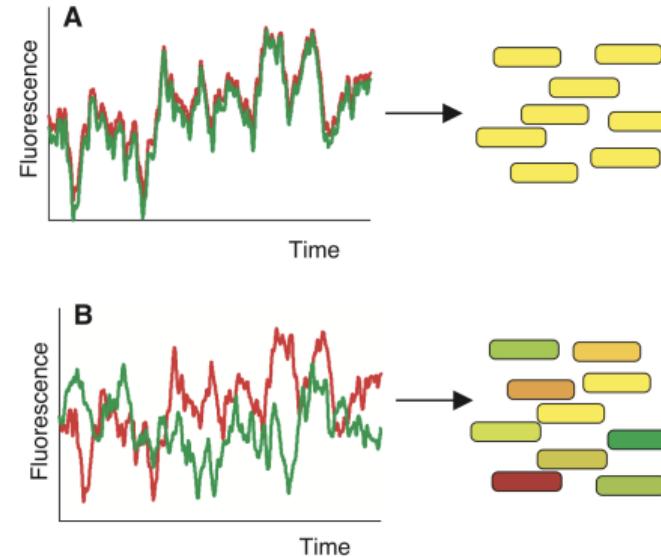
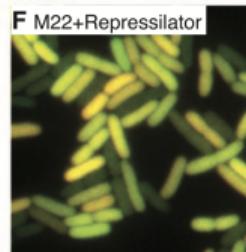
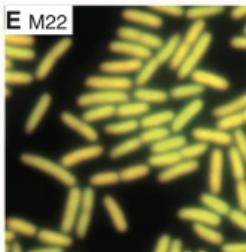
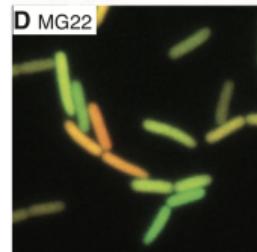
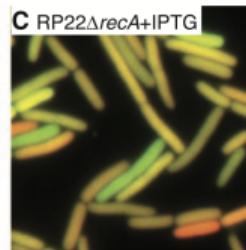
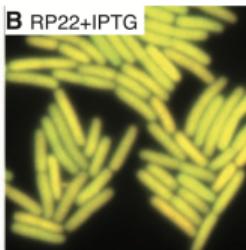
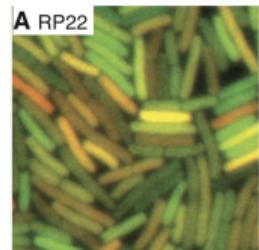


Central dogma of molecular biology



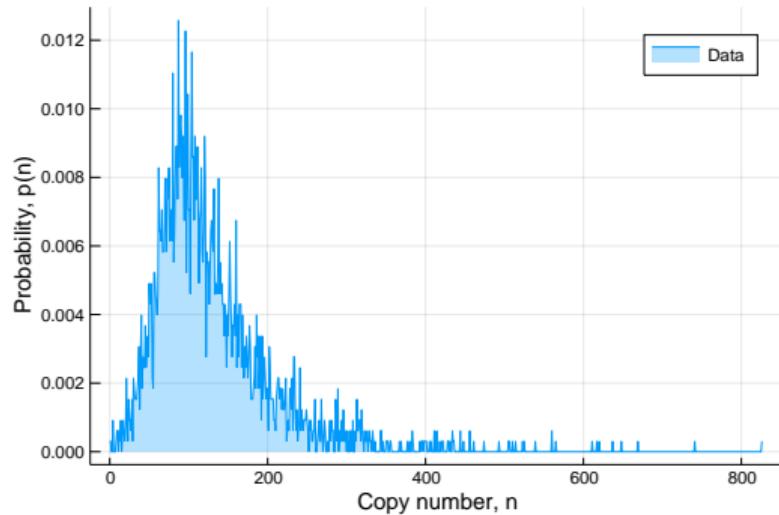
Intrinsic versus extrinsic noise (Elowitz et al, *Science*, 2010)

Variability in protein numbers is present and can be measured...

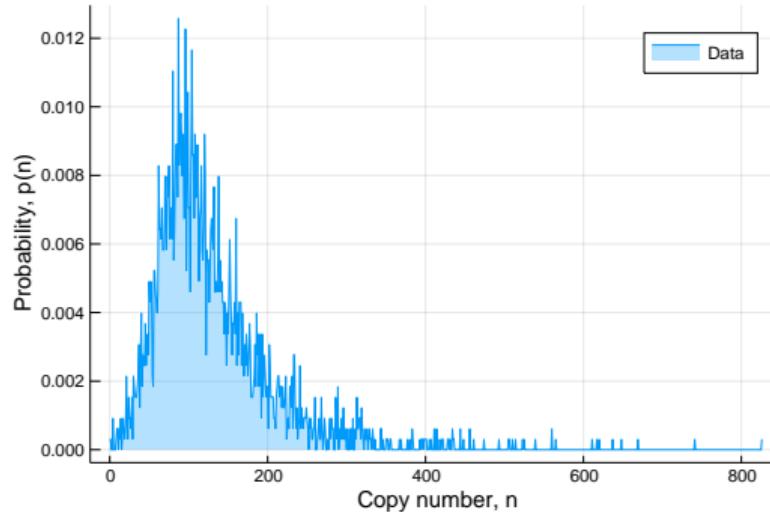


(A) Correlated = extrinsic noise and (B) Uncorrelated = intrinsic noise
(cfp, shown in green; yfp, shown in red)

Heterogeneity in transcriptomic data

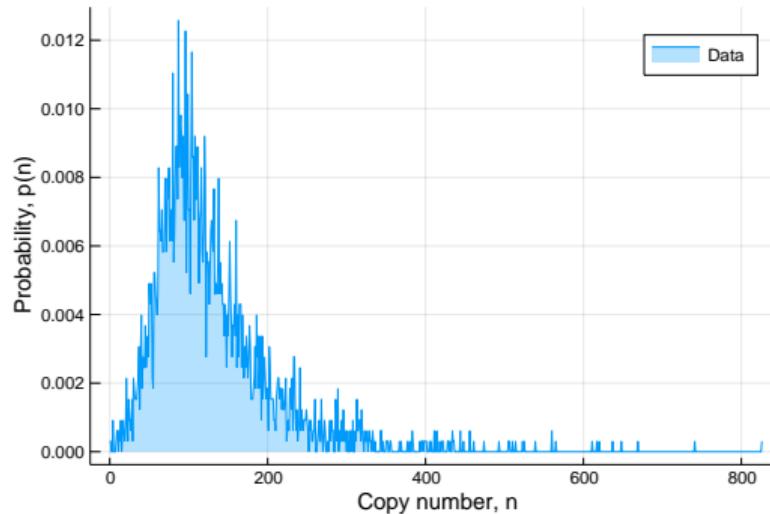


Heterogeneity in transcriptomic data



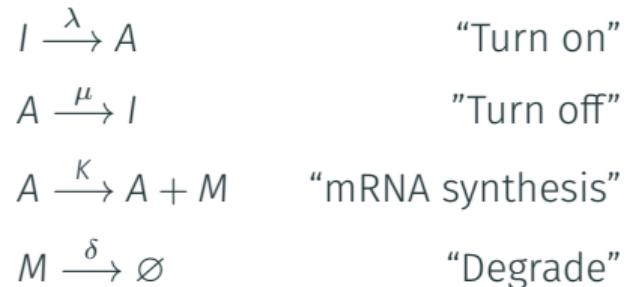
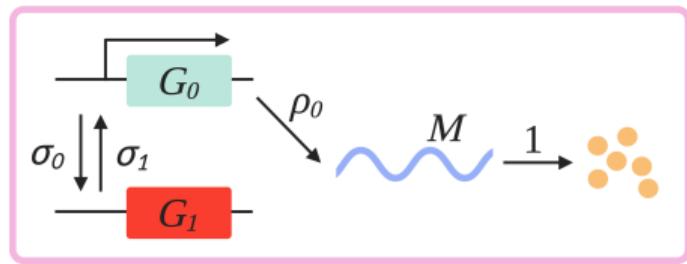
- Temporal information lost in “snapshot” data

Heterogeneity in transcriptomic data



- Temporal information lost in “snapshot” data
- Variation due to inherent stochasticity of the gene transcription process (**intrinsic noise**), as well as external sources (**extrinsic noise**)

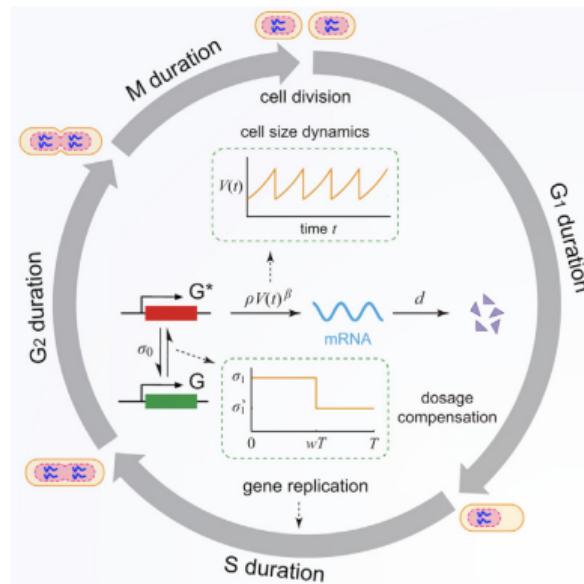
The canonical stochastic model of gene transcription



- Captures some of the variability in gene expression data
- Tractable stationary distribution, useful for building more complex models (eg extrinsic noise, multiple gene states)
- **Limitations:** not particularly biologically realistic and inference can be slow

Overview of workshop

Starting from a simple gene expression model, we will build an archetypal WCM in E. coli



Jia and Grima, *iScience*, 2023

Part 1: 2:00-3:30pm

- Bursty transcription
- Gene switching
- Protein synthesis and degradation
- Autoregulation
- Metabolism (Michaelis-Menten kinetics)

BREAK: 3:30-4:00pm

Part 2: 4:00-5:00pm

- Cell volume effects
- Cell division and DNA replication
- Extrinsic noise