Noise reduction and information transfer in the cell

Glenn Vinnicombe (Dept. of Engineering, Cambridge)
in collaboration with
Johan Paulsson (Harvard Medical School)
Ioannis Lestas (Dept. of Engineering, Cambridge)

Overview

- The cell is a noisy cell, in spite over being packed full of feedback loops.
- Why?

ARTICLES

Fundamental limits on the suppression of molecular fluctuations

Ioannis Lestas[1], Glenn Vinnicombe[1] & Johan Paulsson[2]

REVIEWS

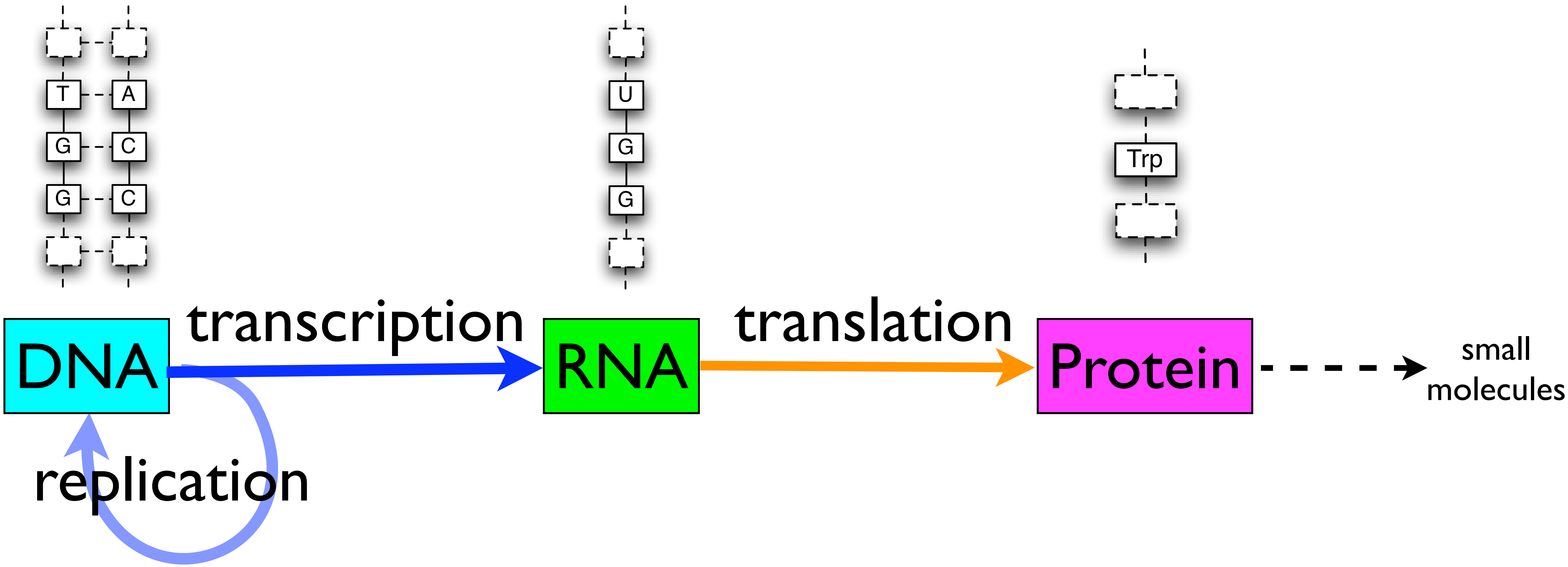
Functional roles for noise in genetic circuits

Avigdor Eldar[1]† & Michael B. Elowitz[1]

Overview

- The cell is a noisy cell, in spite over being packed full of feedback loops.
- Why?
- I shall present some fundamental limitations for biological systems, in terms of minimum achievable variances.
- These limits apply to the regulation of a single species within an arbitrarily complex network, and the suggest that the cost of reducing noise can be extremely high.

The Central Dogma



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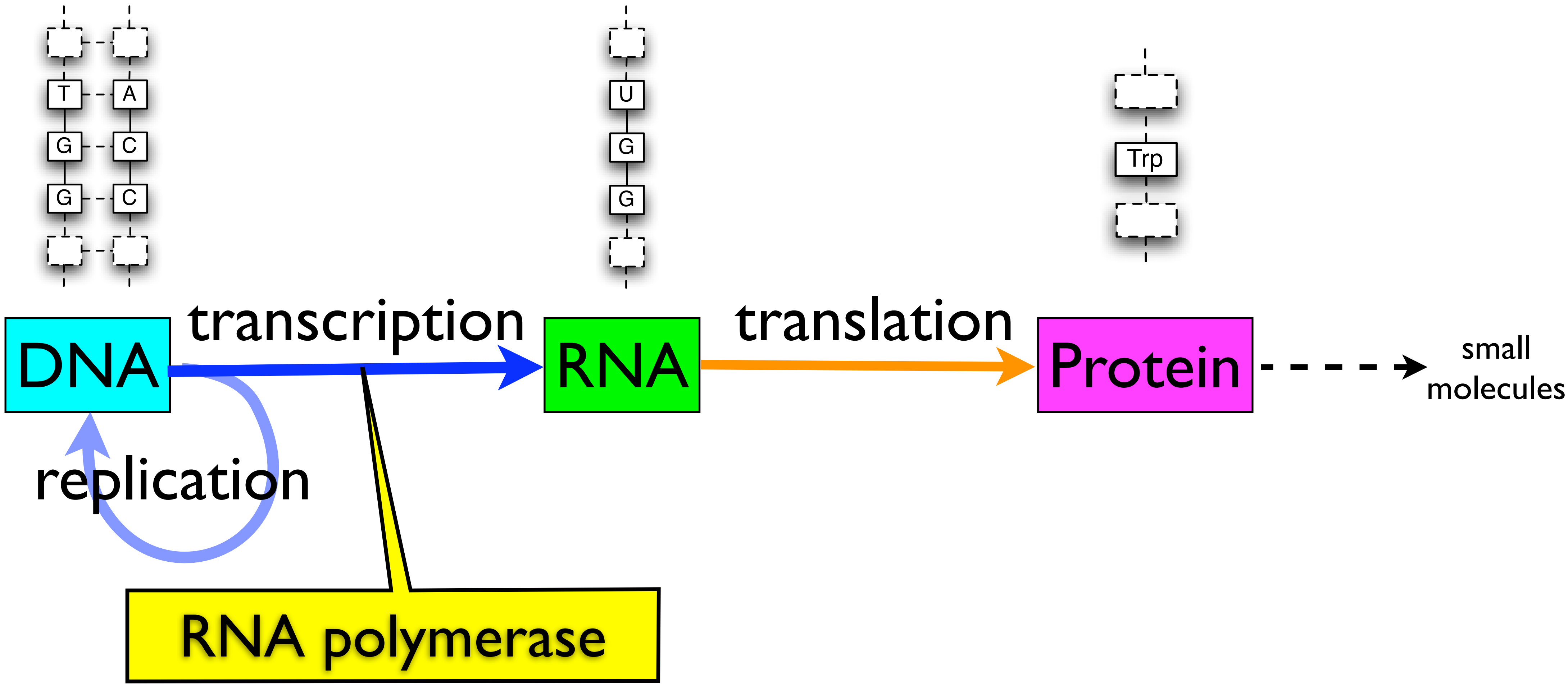
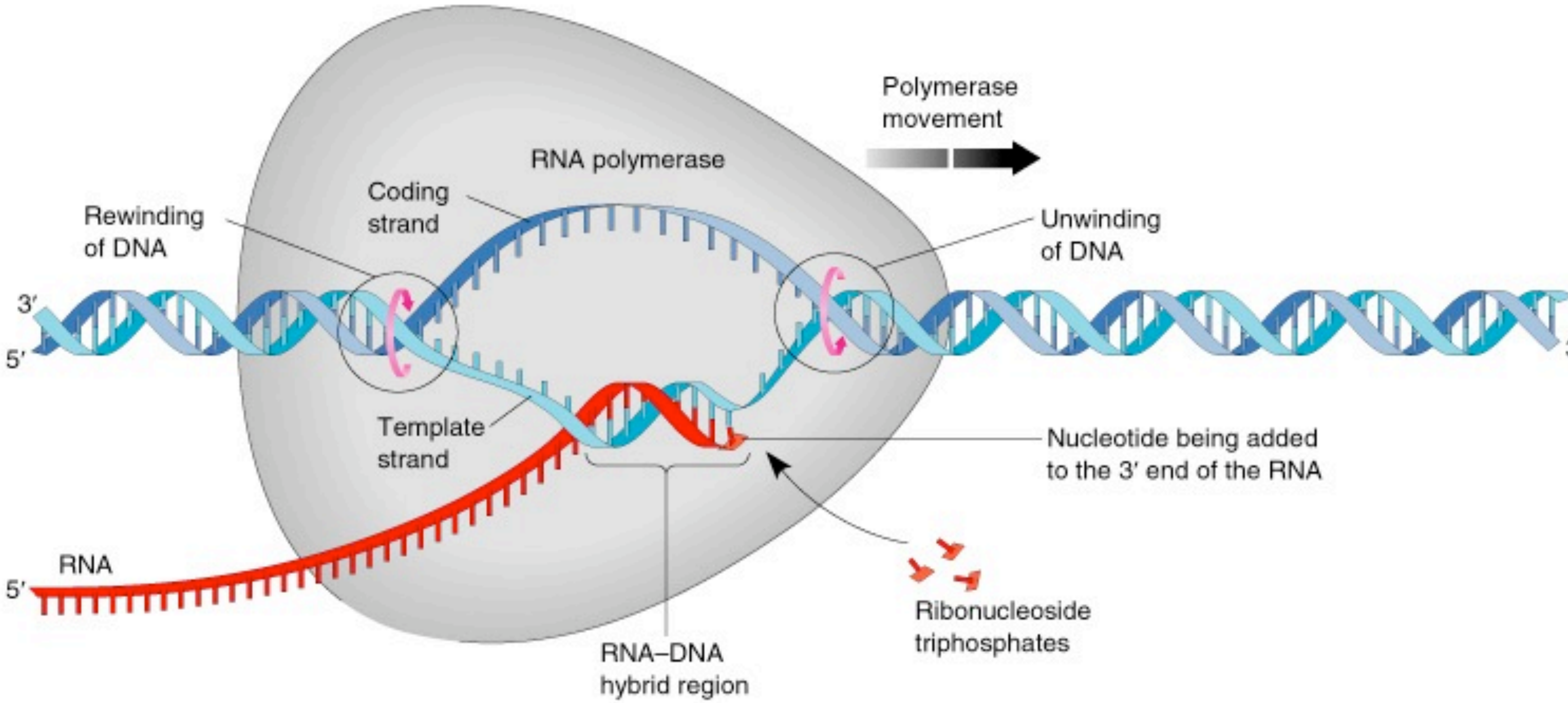


Transcription



1. RNA polymerase slides along the DNA, creating an open complex as it moves.

2. The DNA strand known as the template strand is used to make a complementary copy of RNA as an RNA–DNA hybrid.

3. The RNA is synthesized in a 5′ to 3′ direction using ribonucleoside triphosphates as precursors. Pyrophosphate is released (not shown).

4. The complementarity rule is the same as the A–T and G–C rule except that U is substituted for T in the RNA.

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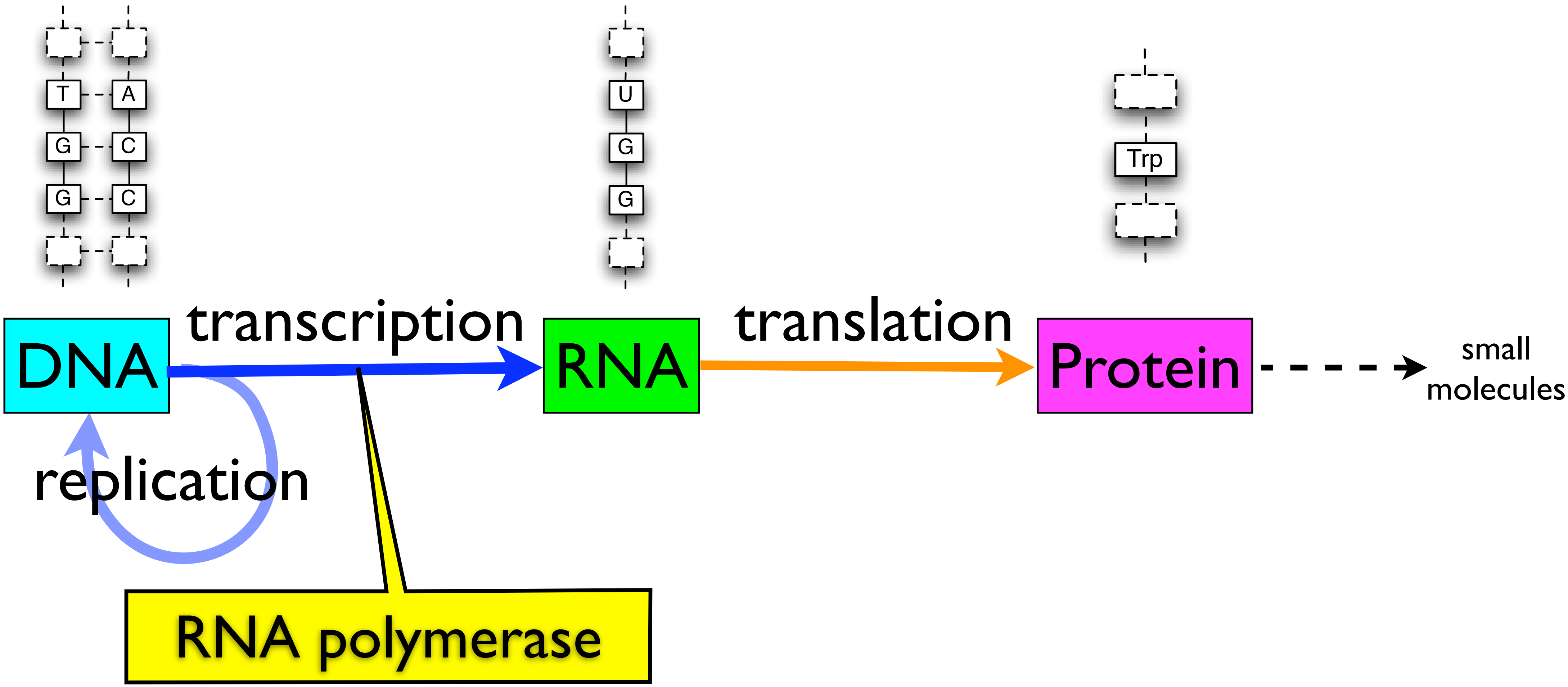

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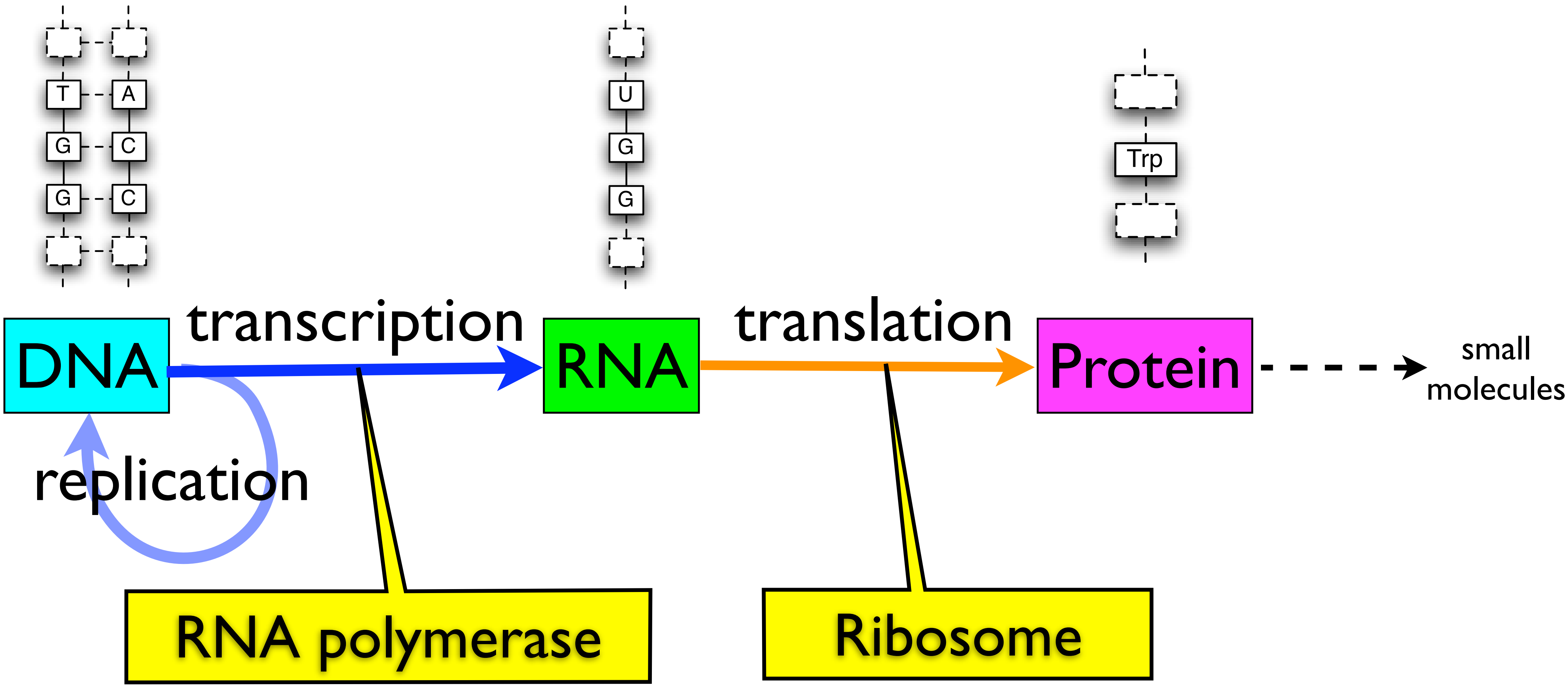
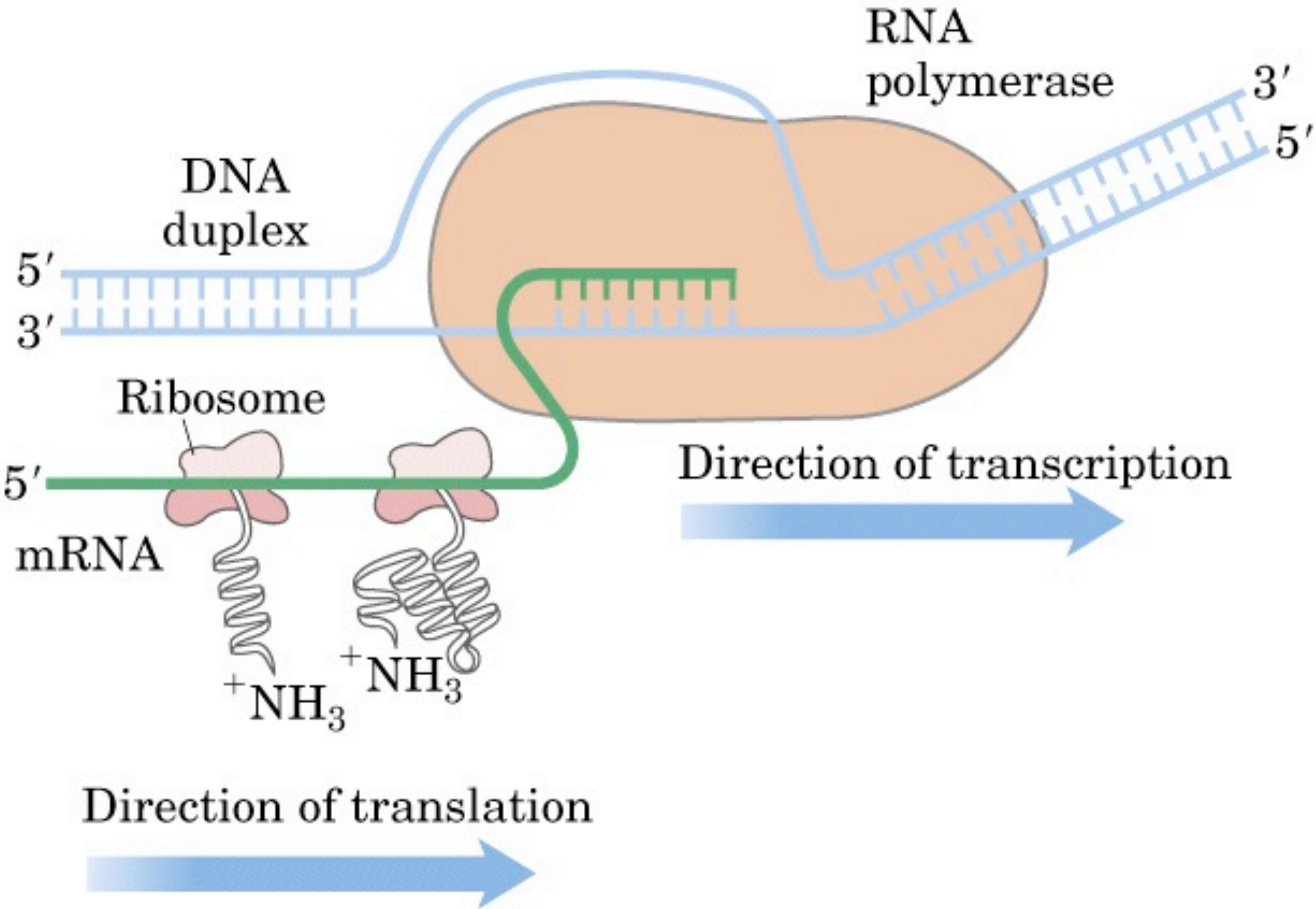
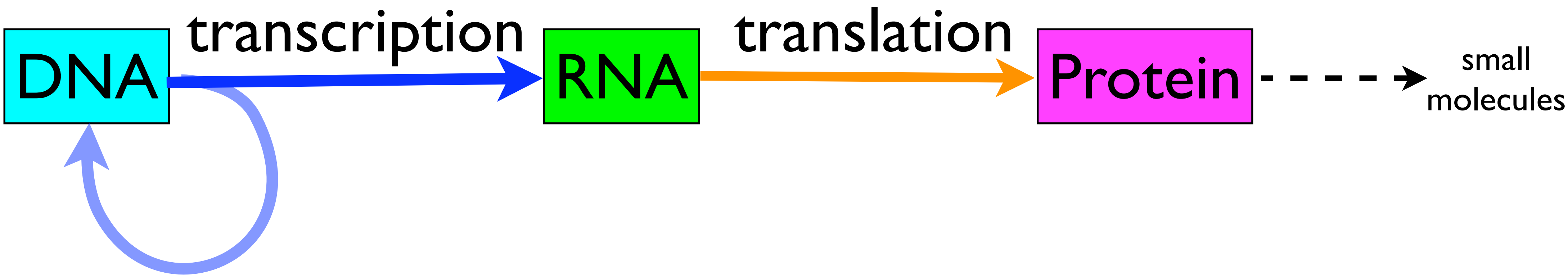


Transcription & Translation in Prokaryotes



Regulation of gene expression



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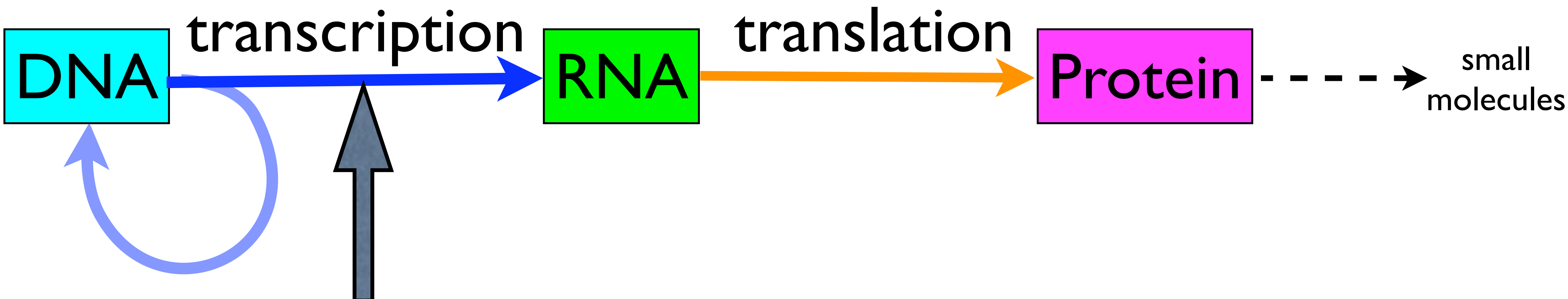


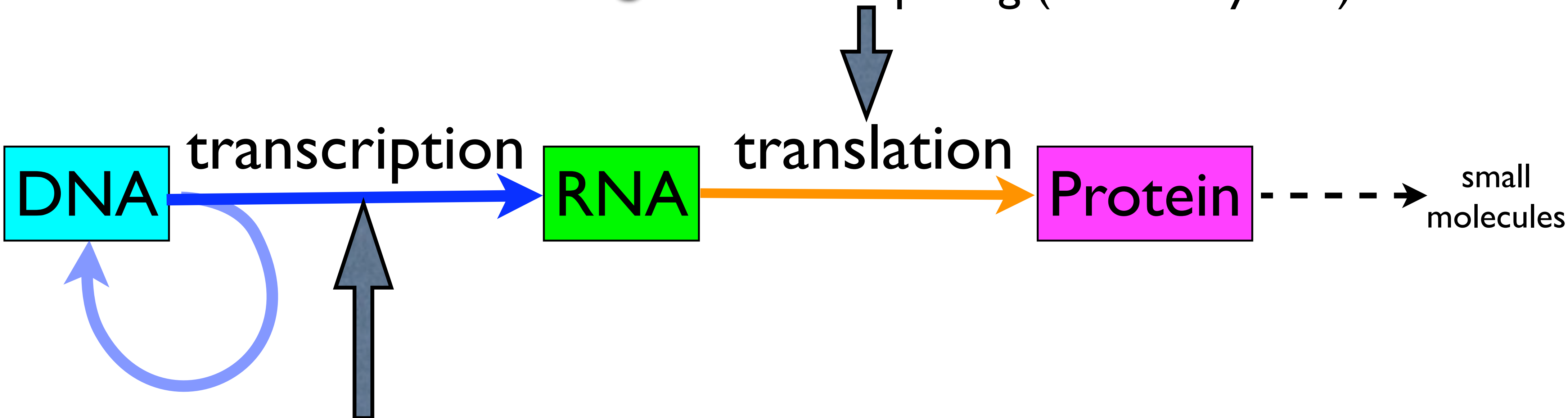
- Gene silencing
- Gene regulation by

DNA binding proteins:

- Activators/repressors
- Sigma factors

Regulation of gene expression

- post-transcriptional control
  - antisense RNA / RNAi
  - temperature sensors
  - RNA binding small molecules
  - control of splicing (in eukaryotes)



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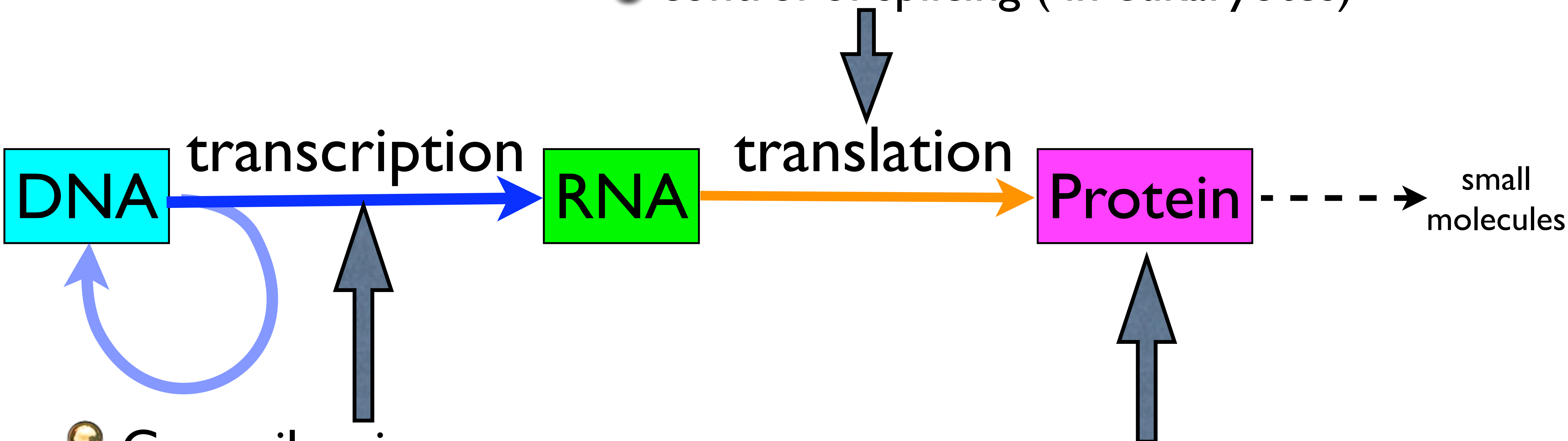

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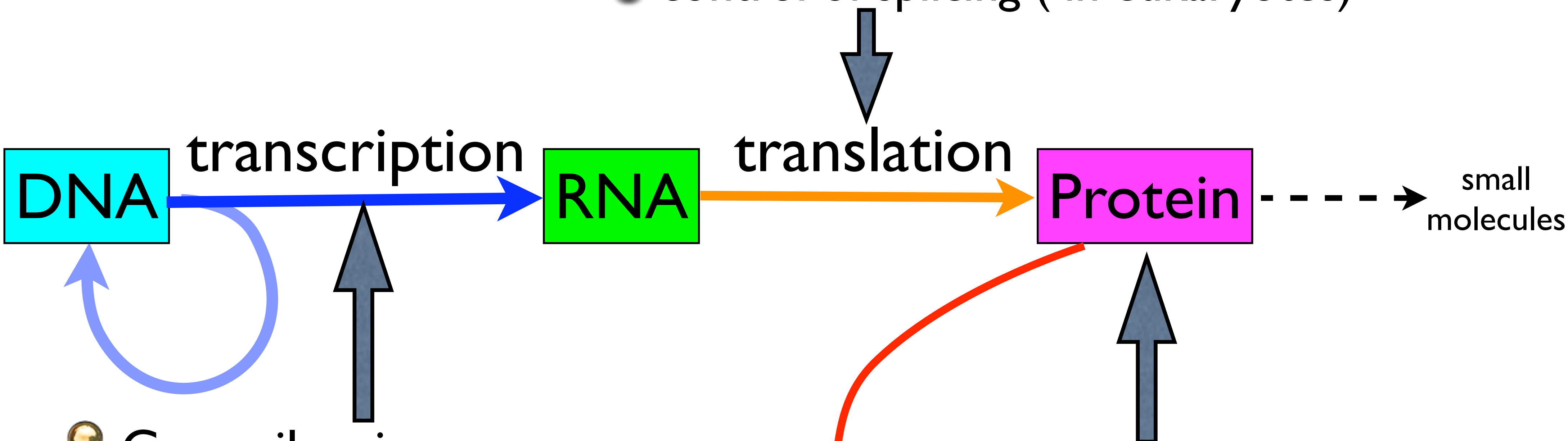

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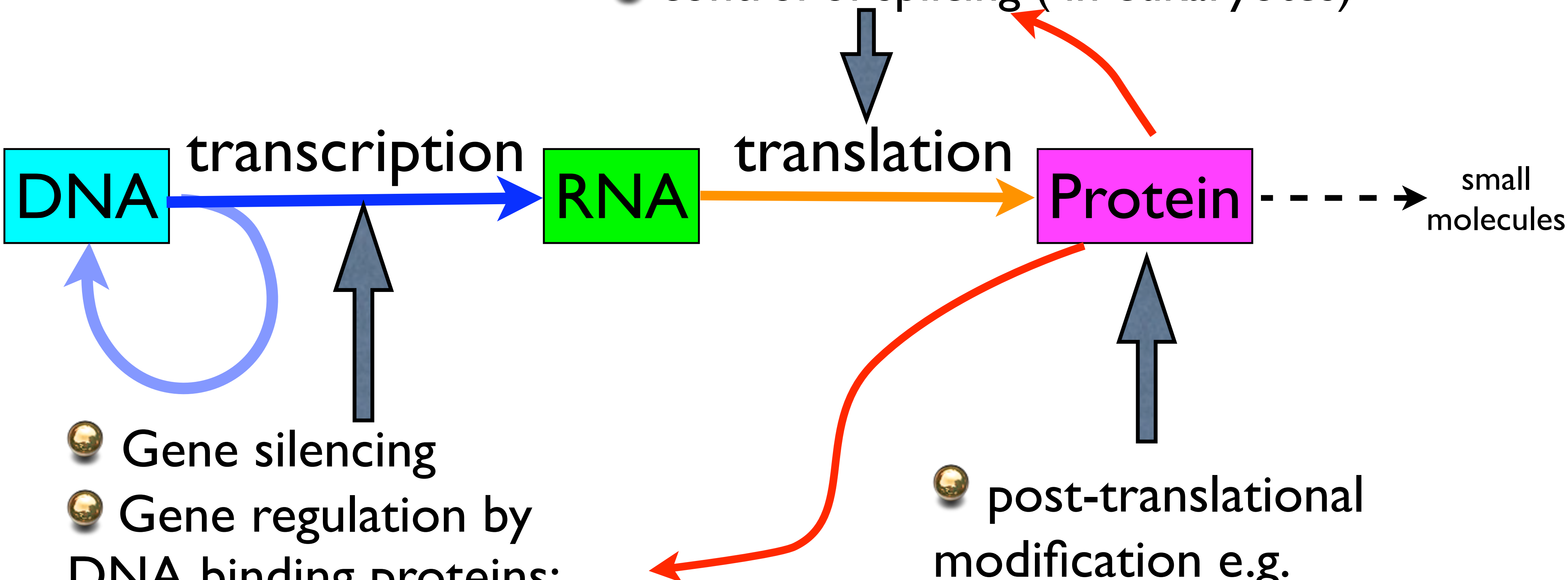

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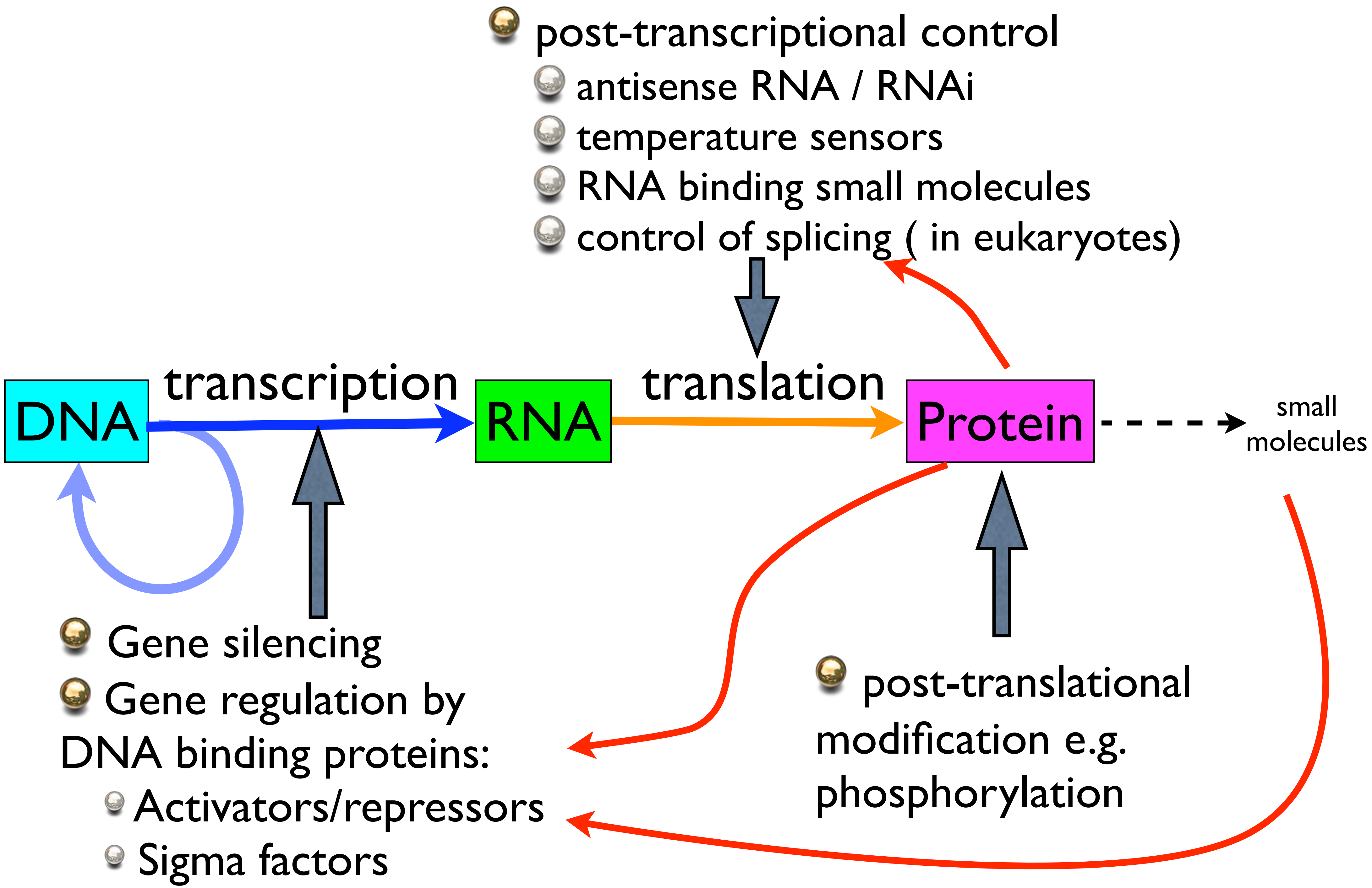

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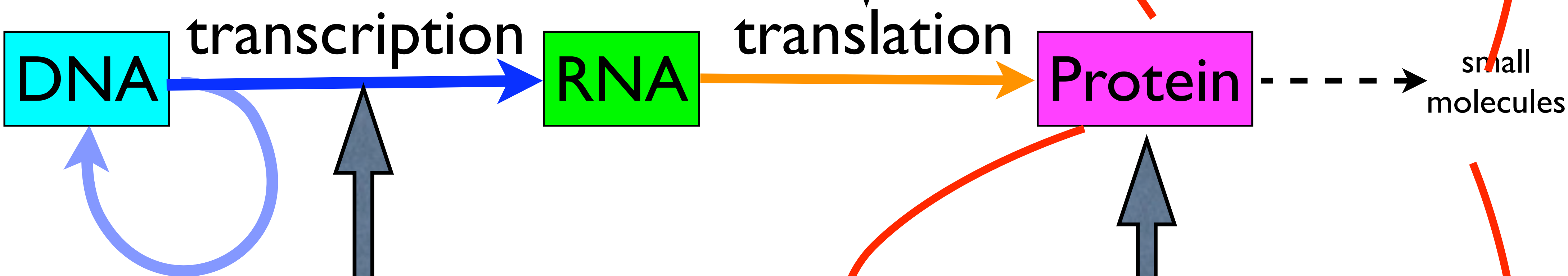

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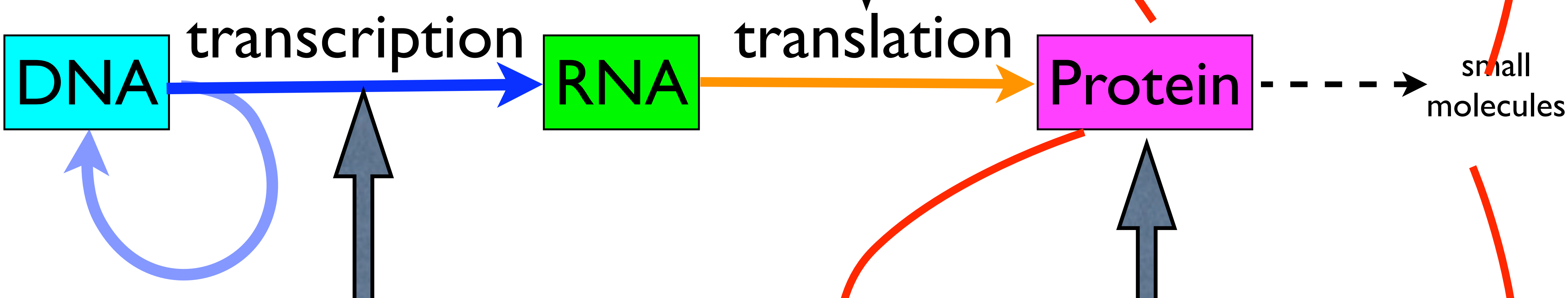
(and this is just part of the story!)



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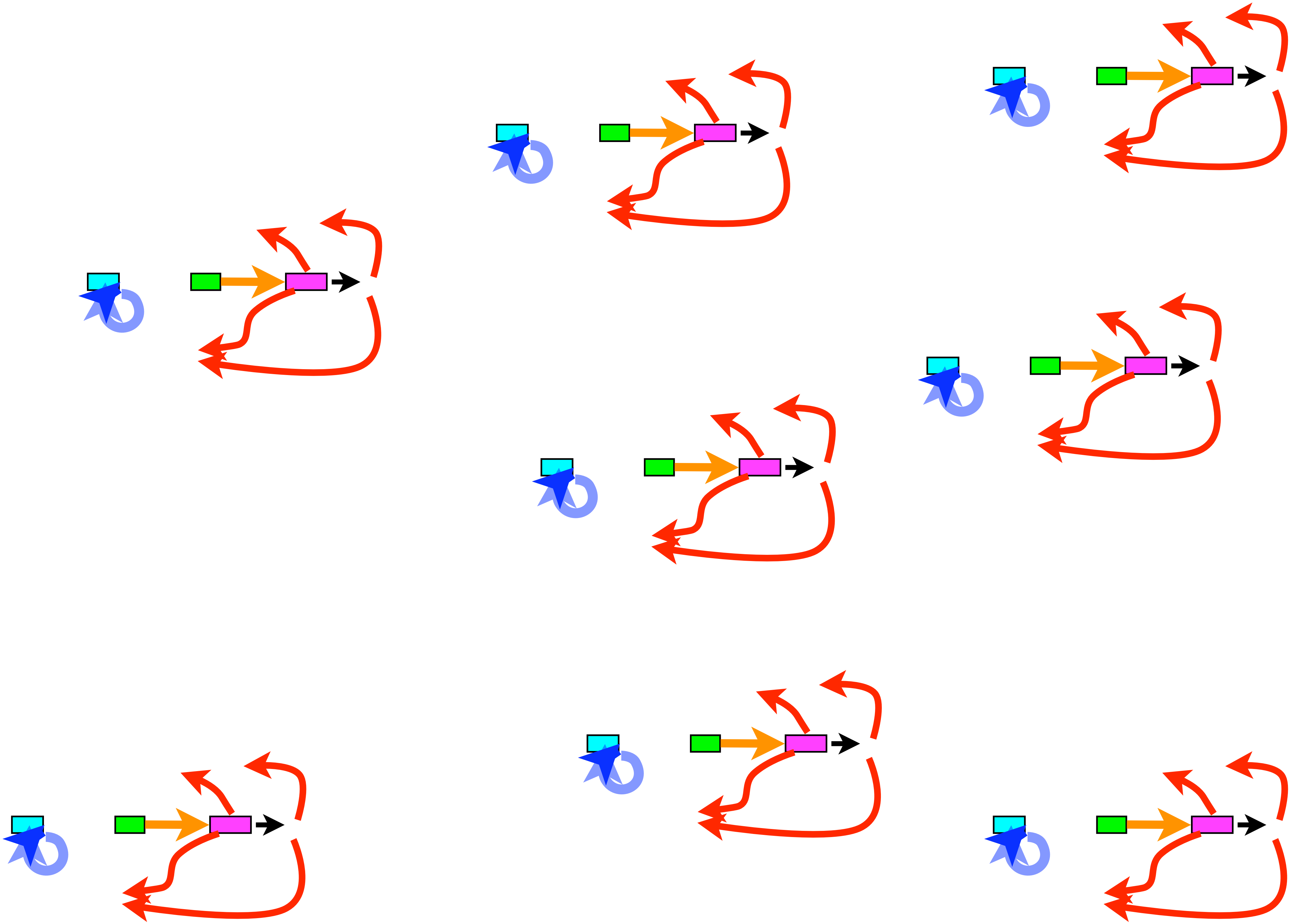
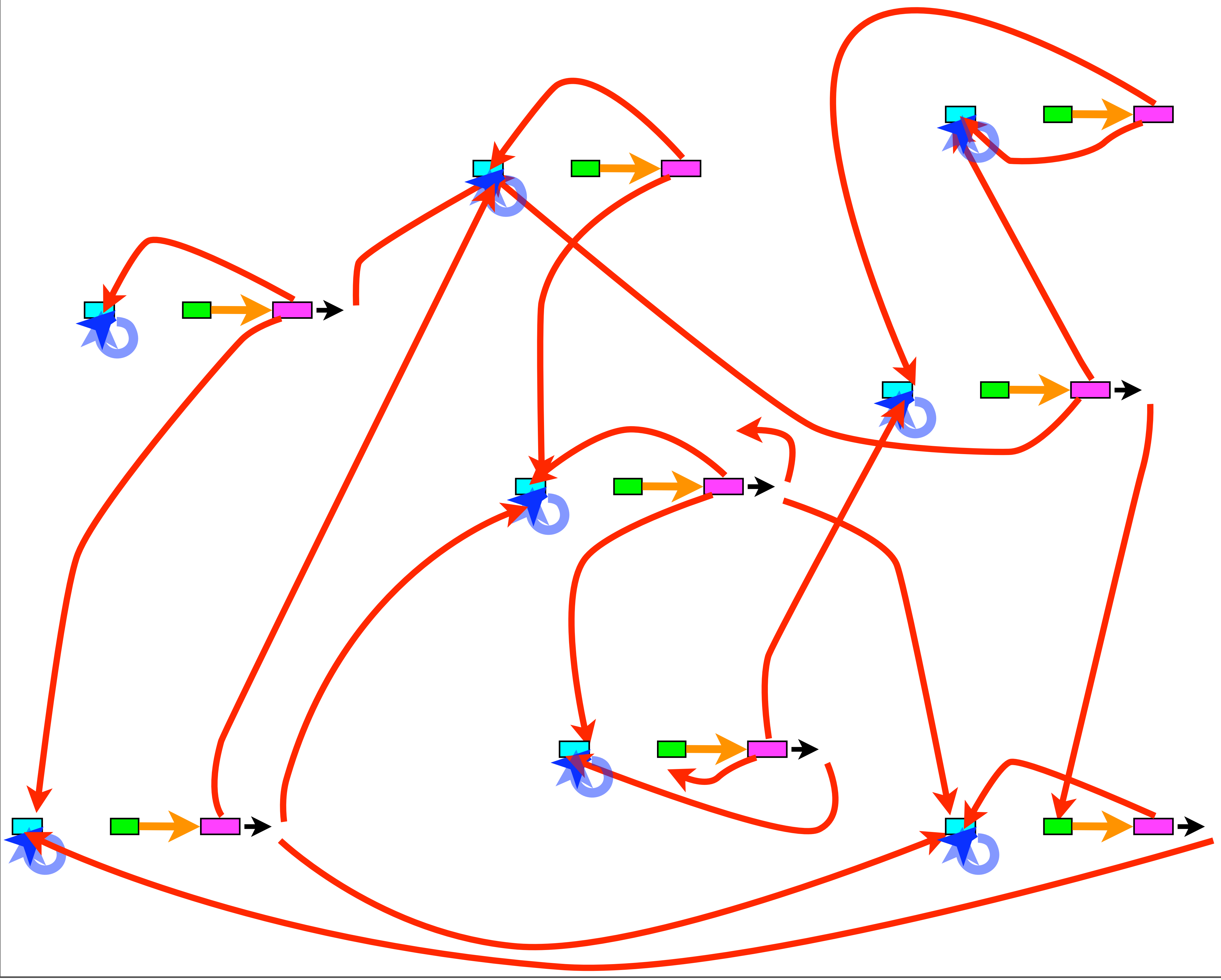
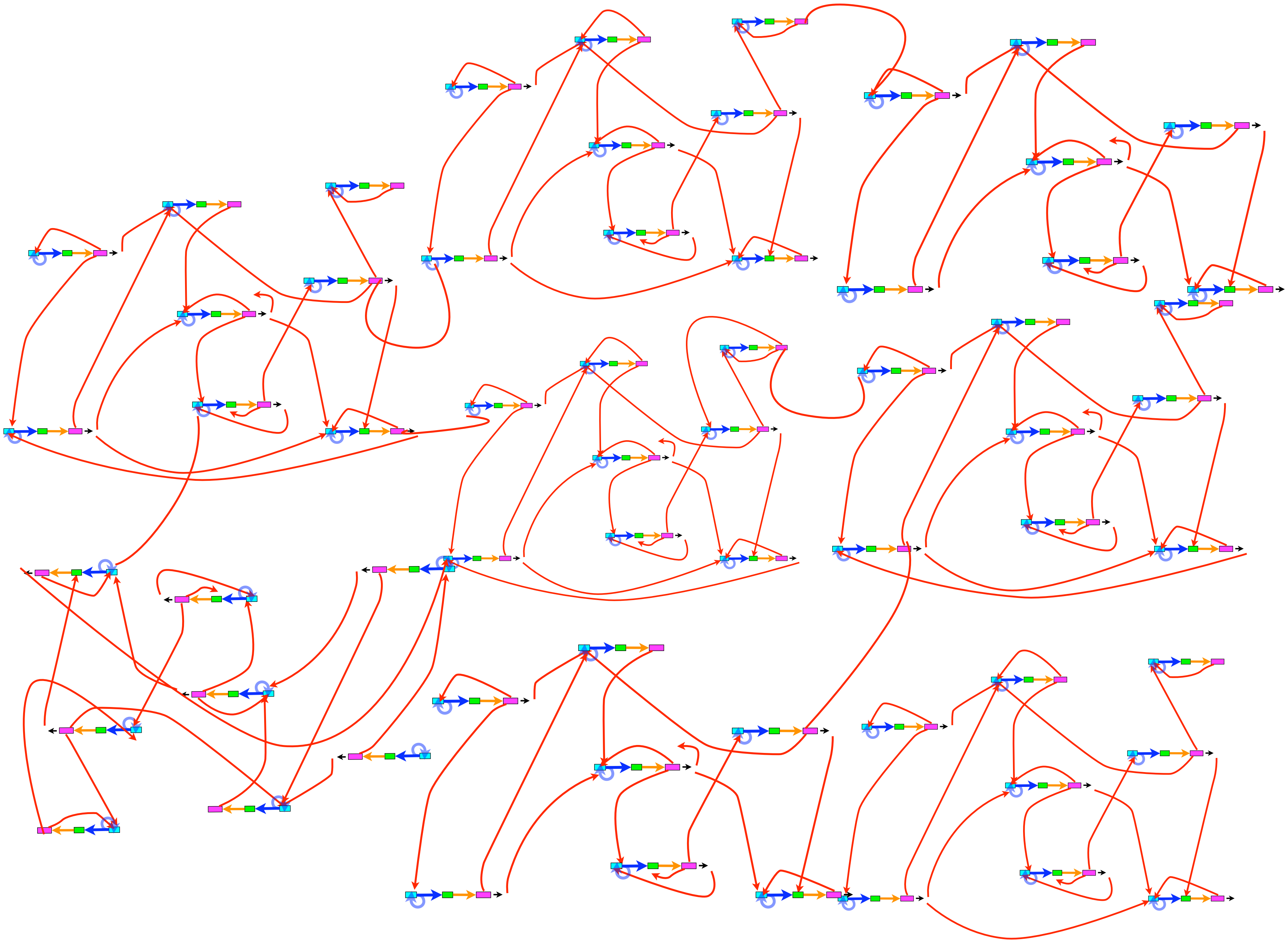
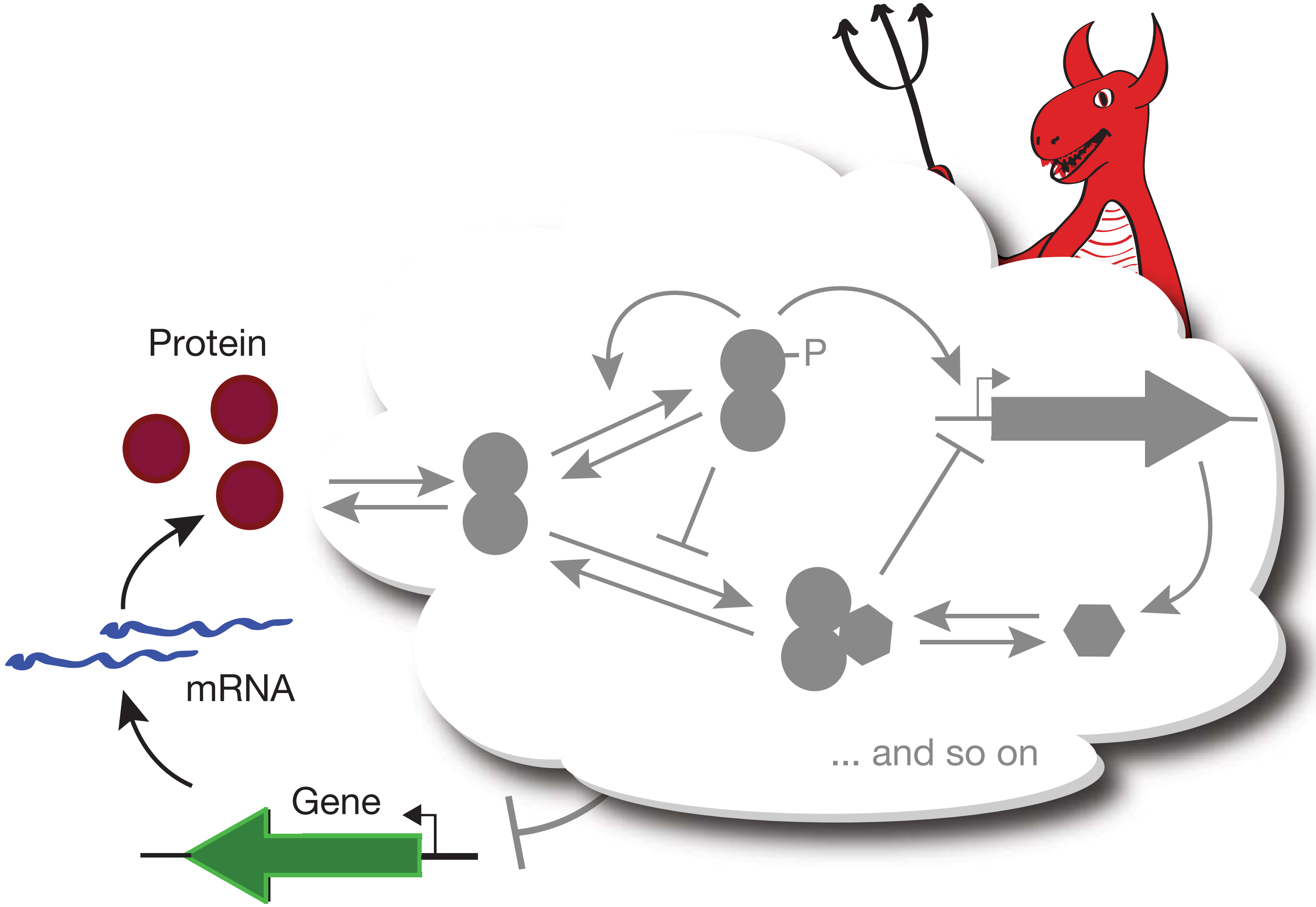


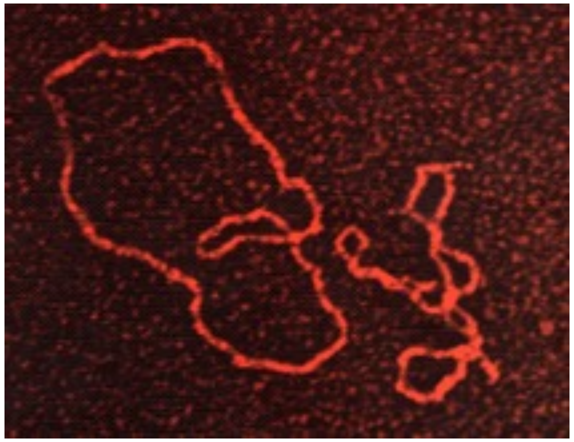


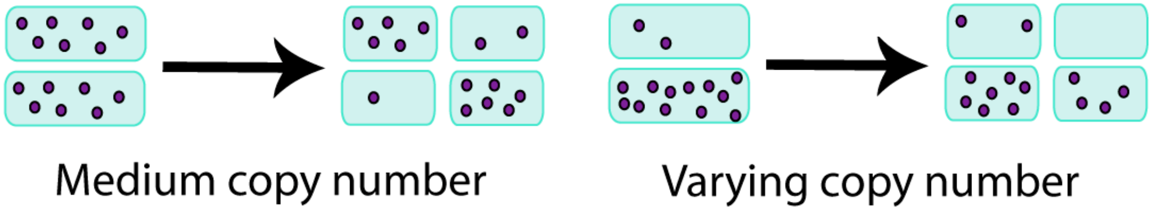


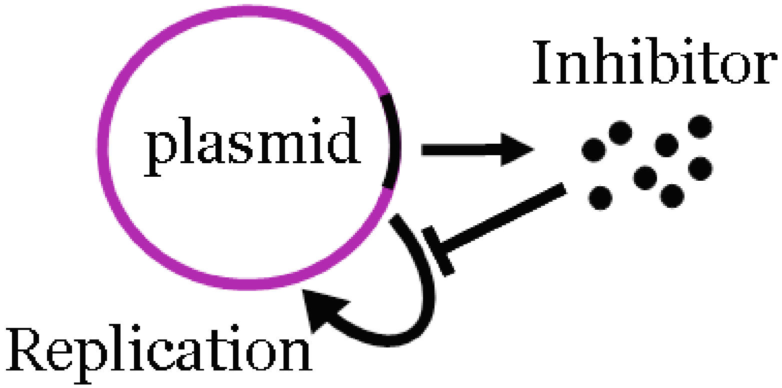

Protein
P
mRNA
Gene
... and so on

Minimizing variance: ColE1 replication control

- Approx 16 plasmid copies per cell
- Partitioned randomly at cell division
- Under strong selection for small variance





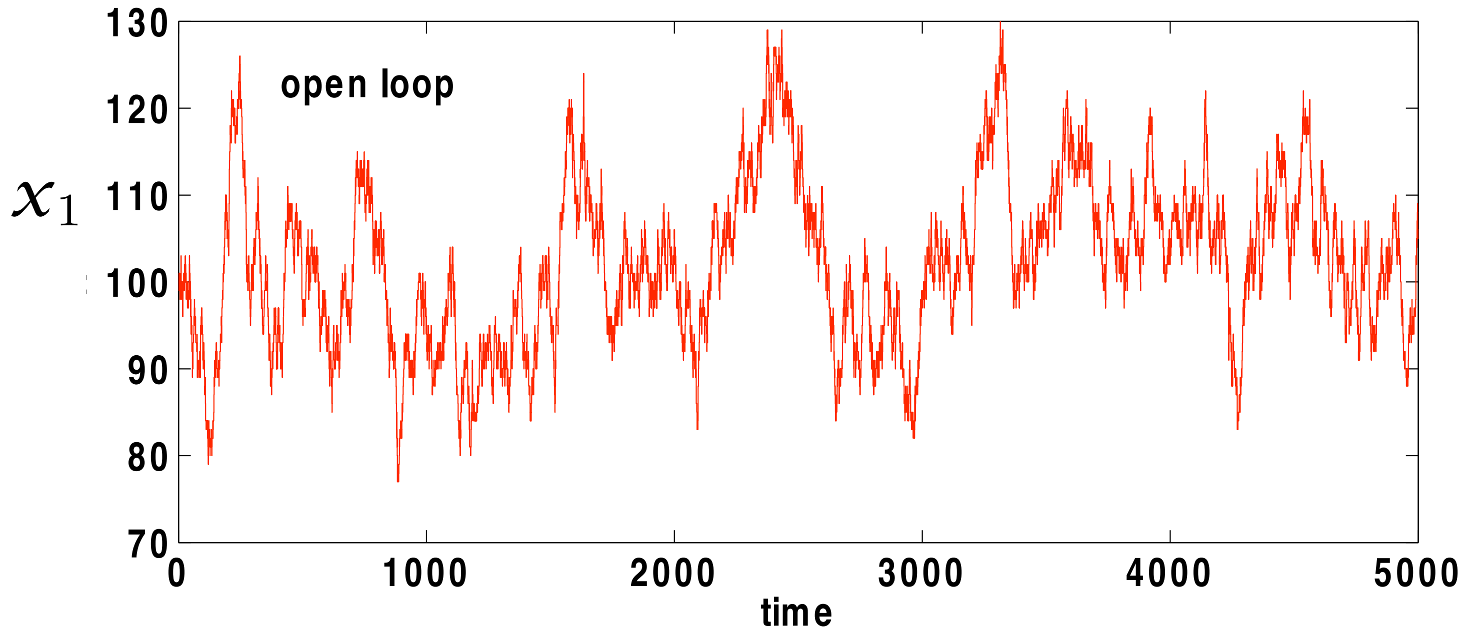


Regulation of molecule numbers

Consider a single species: e.g. mRNA of a constitutively expressed gene

$$x_1 \xrightarrow{c} x_1 + 1$$
$$x_1 \xrightarrow{x_1/\tau_1} x_1 - 1$$

$$\emptyset \underset{k_2}{\overset{k_1}{\leftrightarrows}} X_1$$



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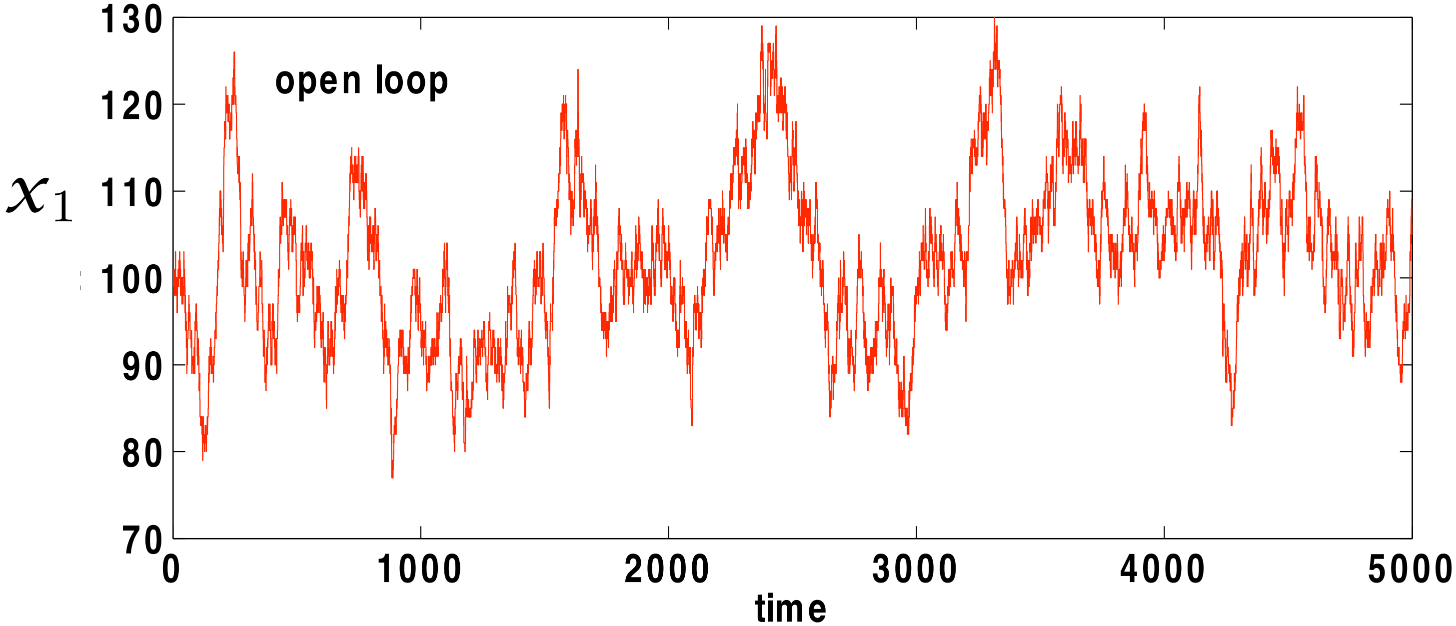
$$\Pr\big(x_1(t+dt) = N + 1 | x_1(t) = N\big) = c\,dt$$



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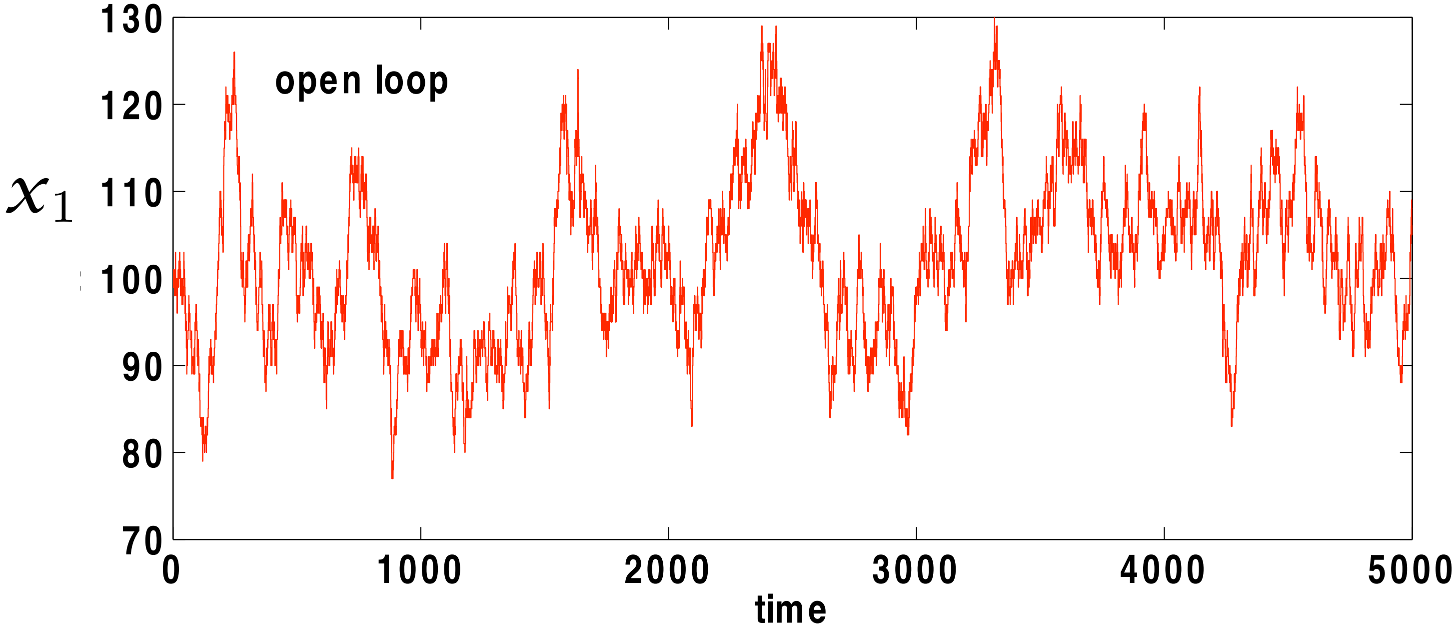
$$\Pr(x_1(t+dt) = N+1 | x_1(t) = N) = c\,dt$$
$$\Pr(x_1(t+dt) = N-1 | x_1(t) = N) = N/\tau_1\,dt$$



$$\sigma_1^2 = \langle x_1 \rangle$$

Regulation of molecule numbers

(with feedback)

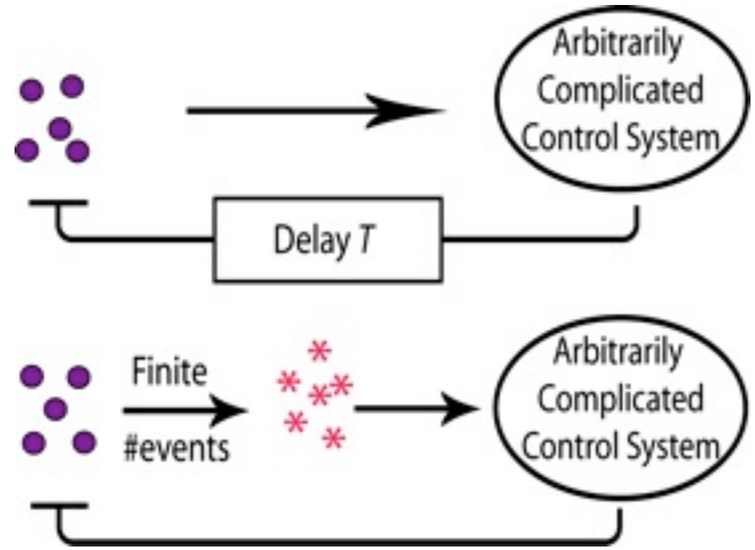
$$x_1 \xrightarrow{u_t} x_1 + 1$$
$$x_1 \xrightarrow{x_1/\tau_1} x_1 - 1$$

where $u_t = f(\{x_1(t') : t' < t\})$

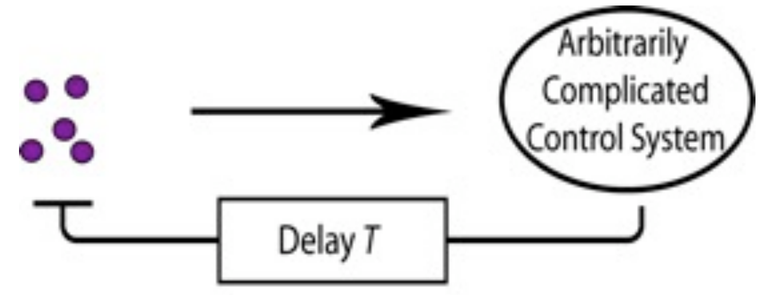
- Can make $\frac{\sigma_1^2}{\langle x_1 \rangle}$ arbitrarily small by appropriate choice of f.

However, limitations are imposed by:

- Delays
- Feedback mechanisms/capacity



Limitations due to delay



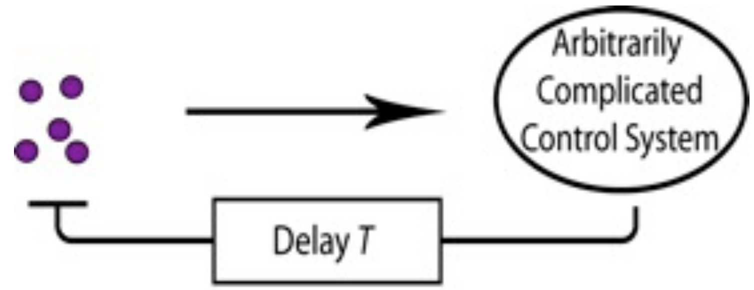
$$x_1 \xrightarrow{u_t} x_1 + 1$$
$$x_1 \xrightarrow{x_1/\tau_1} x_1 - 1$$

where $u_t = f(\{x_1(t') : t' < t - T\})$

Theorem: If x_1 is a stationary process then

$$\frac{\sigma_1^2}{\langle x_1 \rangle} \geq (1 - e^{-2T/\tau_1})$$

Limitations due to delay



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delay

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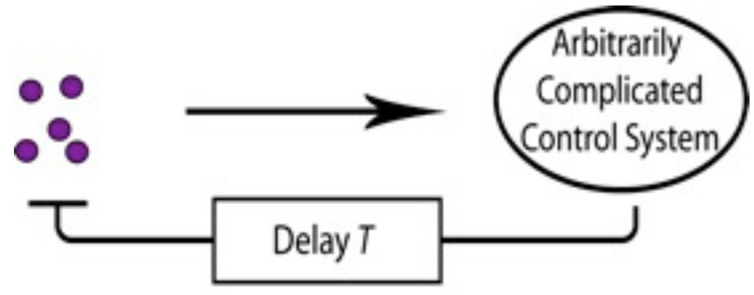

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Theorem: If x_1 is a stationary process then

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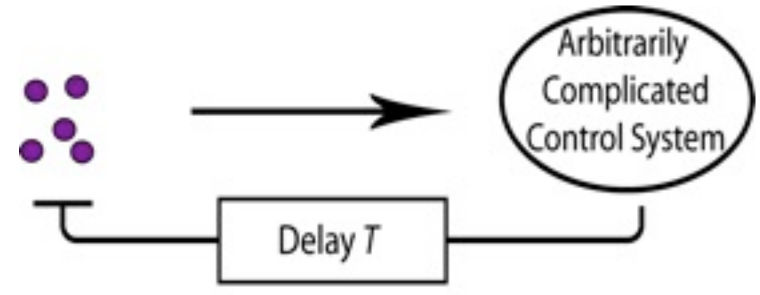
Proof: Let $\mathcal{I}_t = \{x_1(t'), t' < t - T\}$

$$\sigma_1^2 = E[(x_1 - E[x_1])^2] = E[E[x_1 - E[x_1])^2]|I_t]]$$
$$\geq E[E[(x_1 - E[x_1|I_t])^2|I_t]]$$
$$= E[E[x_1|\mathcal{I}_t] - x_1(t-T)e^{-2T/\tau_1}]$$

Limitations due to delay



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Theorem: If x_1 is a stationary process then

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On the other hand, if

$$x_1 \xrightarrow{u_t x_1} x_1 + 1$$
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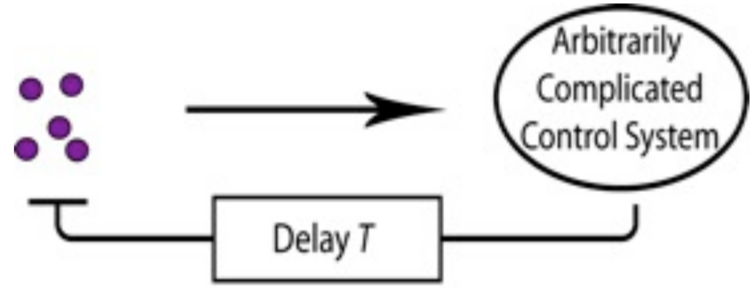
then

$$\frac{\sigma_1^2}{\langle x_1 \rangle} \geq 2T/\tau_1$$

Limitations due to delay



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delay

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Theorem: If x_1 is a stationary process then

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replication

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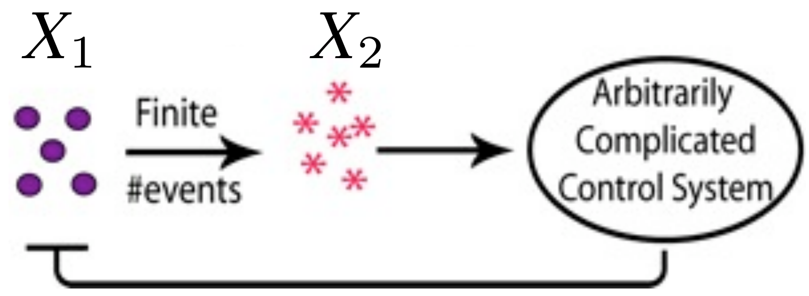
then

$$\frac{\sigma_1^2}{\langle x_1 \rangle} \geq 2T/\tau_1$$

Limitations due to mechanisms: molecular channels



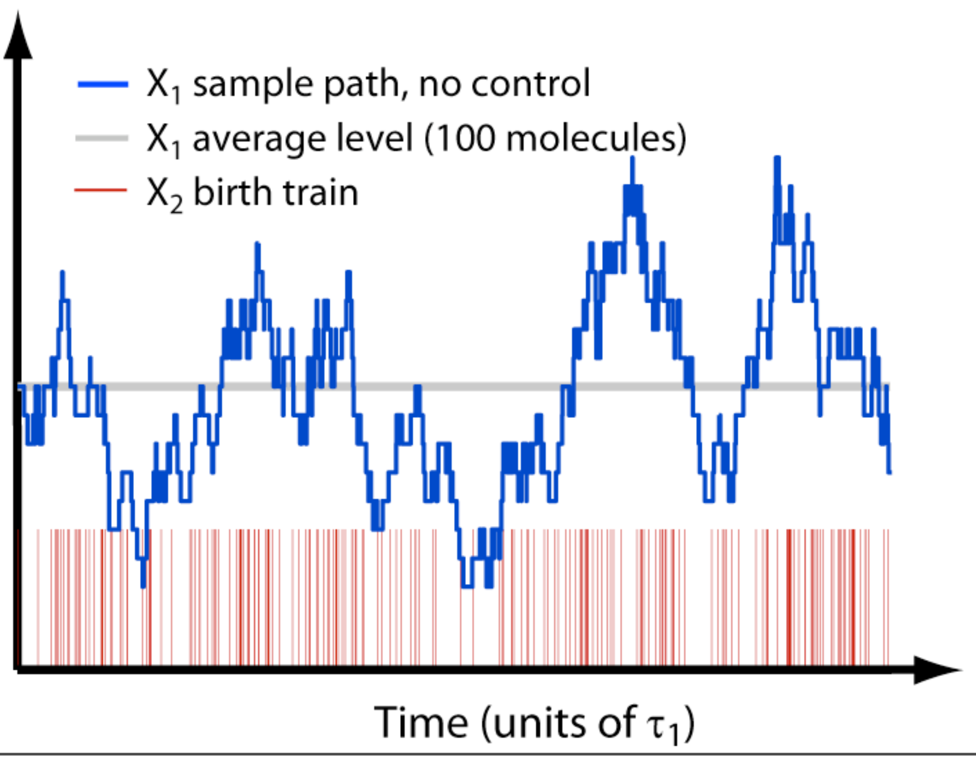
System:

$$x_1 \xrightarrow{u_t} x_1 + 1$$
$$x_1 \xrightarrow{x_1/\tau_1} x_1 - 1$$

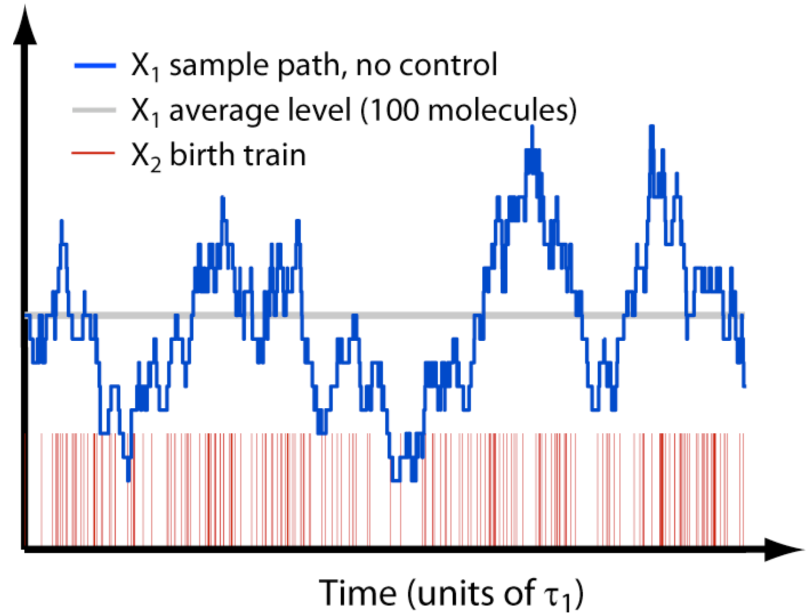
Sensor:

$$x_2 \xrightarrow{\alpha x_1} x_2 + 1$$
$$x_2 \xrightarrow{x_2/\tau_2} x_2 - 1$$

where $u_t = f(\{x_2(t') : t' < t\})$



What is the capacity of a molecular channel?



Consider the channel:

$$x_2 \xrightarrow{z} x_2 + 1$$

$$x_2 \xrightarrow{x_2/\tau_2} x_2 - 1$$

- Capacity is related to that for a photon counting channel (but depends on what constraints are put on z)
- One answer is $C = \langle z \rangle \log\left(1 + \frac{\sigma_z^2}{\langle z \rangle^2}\right) \leq \frac{\sigma_z^2}{\langle z \rangle}$ (nat/s)

$= 1.443\sigma_z^2/\langle z \rangle$ bit/s

(where $C = \max_z I(x_2; z)$)

Feedback capacity and variance

Taking the diffusion approximation of the replication case:

$$x_1 \xrightarrow{u_t x_1} x_1 + 1$$
$$x_1 \xrightarrow{x_1/\tau_1} x_1 - 1$$

$$dx_1 = u_t \langle x_1 \rangle dt + \sqrt{2\langle x_1 \rangle / \tau_1}\, dw$$

gives (Gorbunov and Pinsker '74)

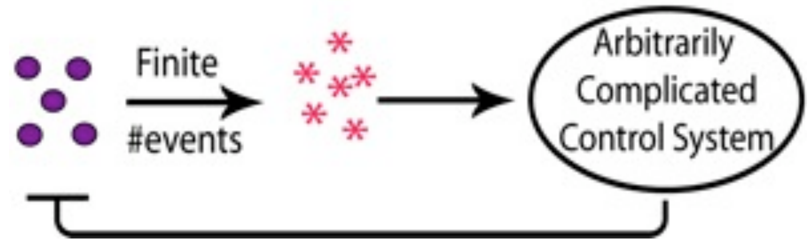
$$\frac{\sigma_1^2}{\langle x_1 \rangle} \geq \frac{1}{C\tau_1} \qquad (\text{for } I(u; x_1) \leq C)$$

Putting this together with the bound on C gives:

$$\frac{\sigma_1^2}{\langle x_1 \rangle} \geq \sqrt{\frac{N_1}{N_2}}$$

where $N_2 = \langle x_2 \rangle \tau_1 / \tau_2 =$ no of molecules of X_2 made per lifetime of X_1.
$N_1 = \langle x_1 \rangle =$ no of molecules of X_1 made per lifetime of X_1.

Summary: Limitations due to channel capacity



System: $x_1 \xrightarrow{u_t x_1} x_1 + 1$, $x_1 \xrightarrow{x_1/\tau_1} x_1 - 1$ $\Rightarrow$ $dx_1 = u_t\langle x_1\rangle dt + \sqrt{2\langle x_1\rangle/\tau_1}\, dw$

Sensor: $x_2 \xrightarrow{\alpha x_1} x_2 + 1$, $x_2 \xrightarrow{x_2/\tau_2} x_2 - 1$

where $u_t = f(\{x_2(t') : t' < t\})$

$$\frac{\sigma_1^2}{\langle x_1\rangle} \geq \sqrt{\frac{N_1}{N_2}}$$

where $N_2 = \langle x_2\rangle \tau_1/\tau_2 =$ no of molecules of X_2 made per lifetime of X_1.
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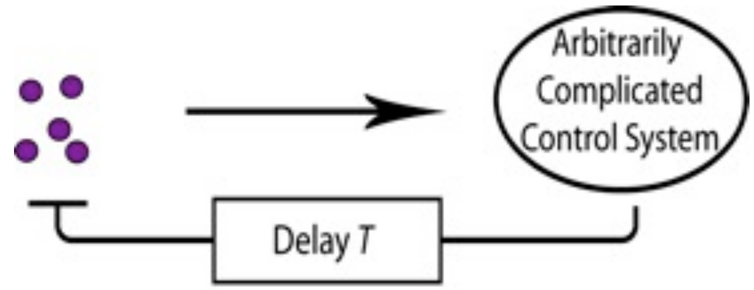
Summary: Limitations due to delay



$$x_1 \xrightarrow{u_t x_1} x_1 + 1$$
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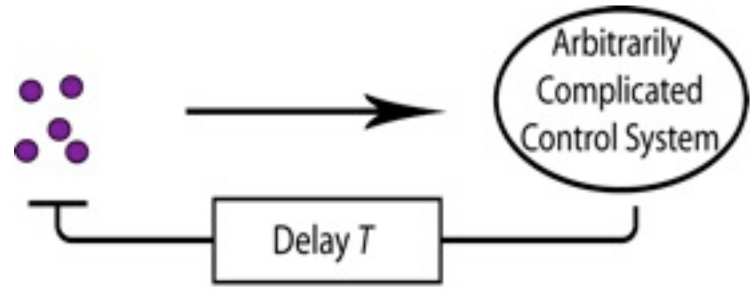
where $u_t = f\left(\{x_1(t') : t' < t - T\}\right)$

If x_1 is a stationary process then

$$\frac{\sigma_1^2}{\langle x_1 \rangle} \geq 2\frac{T}{\tau_1}$$

Summary: Limitations due to delay



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where $u_t = f(\{x_1(t') : t' < t - T\})$

If x_1 is a stationary process then

$$\frac{\sigma_1^2}{\langle x_1 \rangle} \geq 2\frac{T}{\tau_1}$$

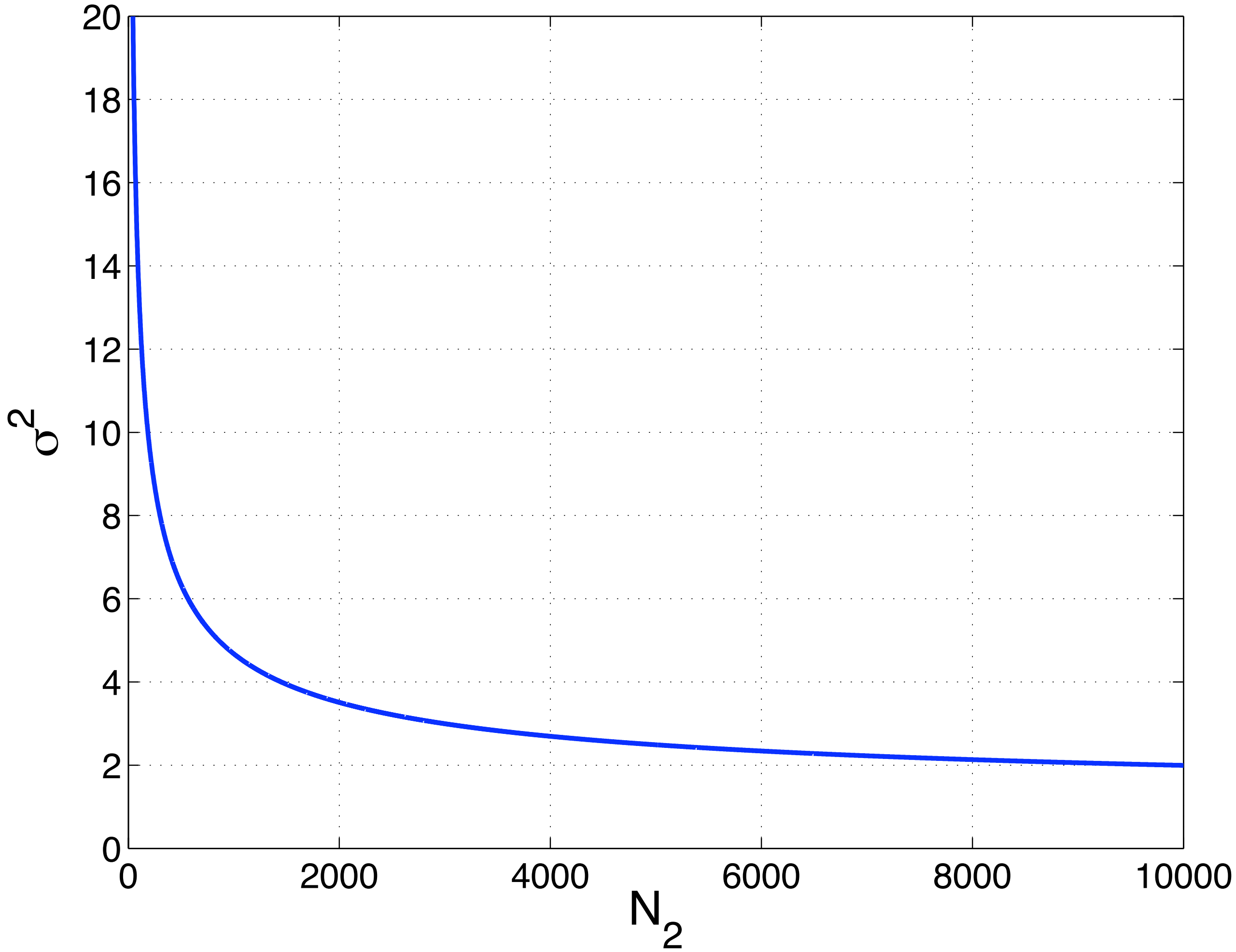
Can combine bounds:

$$\frac{\sigma_1^2}{\langle x_1 \rangle} \geq \frac{T}{\tau_1} + \sqrt{\frac{N_1}{N_2} + \left(\frac{T}{\tau_1}\right)^2}$$

Some numbers

For ColE1, assuming a mean of 16 copies immediately after cell division

- Lower bound due to delays only ($T = 44$): $\sigma^2 \gtrsim 1$
- 10000 inhibitors/cell cycle: $\sigma^2 \gtrsim 2$



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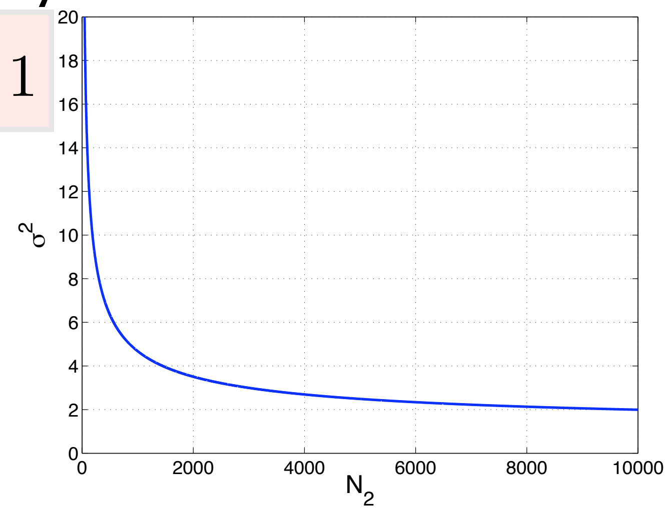
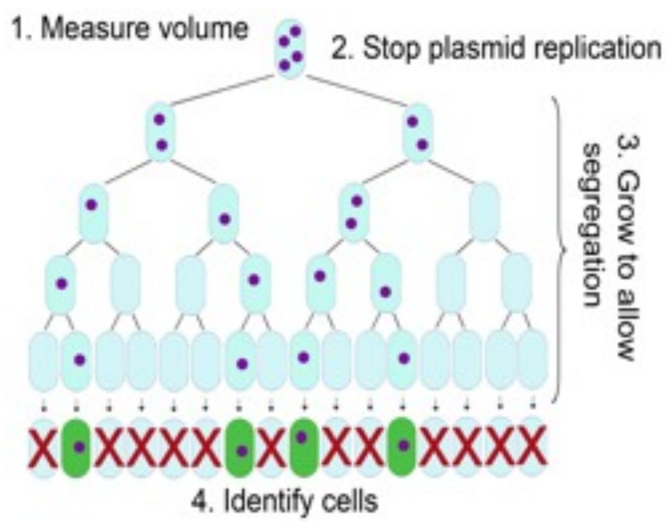
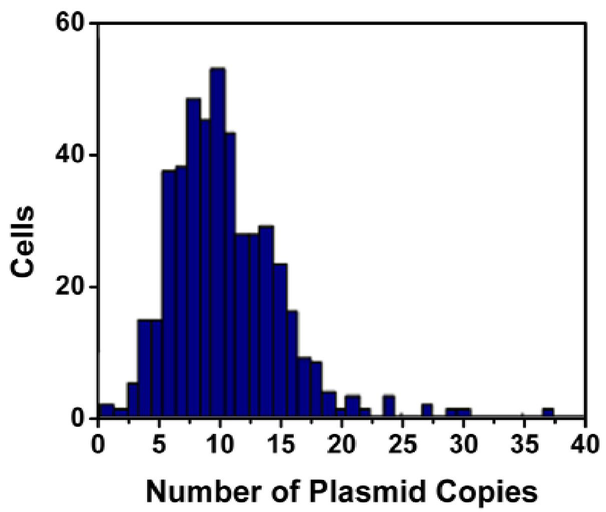


- Early experimental results (Paulsson) suggest $\sigma^2 < 4$ (*although for a different plasmid with the same copy number*).





Extensions

Similar results hold for non-replication case (e.g. transcription/translation:

$$x_1 \xrightarrow{u_t} x_1 + 1$$

e.g.

$$\frac{\sigma_1^2}{\langle x_1 \rangle} \geq \frac{2}{1+\sqrt{1+4N_2/N_1}}, \quad 1 - \exp(-2T/\tau_1)$$

and for nonlinear use of channel:

$$x_2 \xrightarrow{f(x_1)} x_2 + 1$$

(e.g. Hill functions $f(x_1) = v\frac{x_1^H}{K + x_1^H}$)

same bounds, but with $N_2 \rightarrow \gamma N_{2\mathrm{max}}$

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  - and new theory is now also inspiring biological questions!