A unifying autocatalytic network-based framework for bacterial growth laws

Anjan Roy[1], Dotan Goberman[1], Rami Pugatch[1]

[1]Dept. of Industrial Engineering and Management

.Ben-Gurion University of the Negev, Israel

Take Home Message

Cell as an ecology of self-replicating molecular machines with the von Neuman's architecture. Universal constructor = transcription translation machinery.

- Any essential element has two associated growth laws

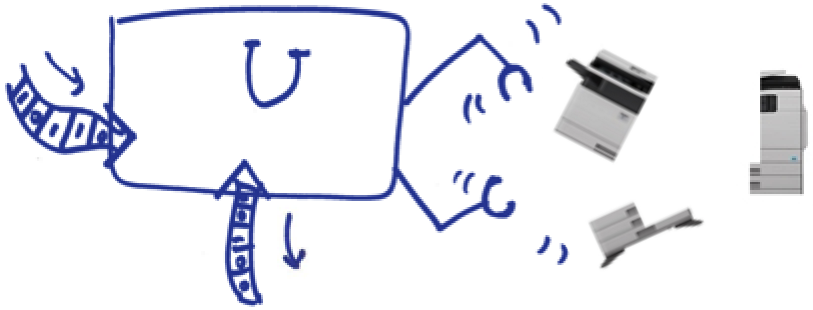
- Going beyond the ribocentric view, we derive new growth laws e.g. RNA-Polymerase growth law

- Growth laws are a manifestation of the conservation of matter, i.e., somewhat uninteresting. The challenge - understand the controls and processing of information from external cues!

Nontrivial self-replication

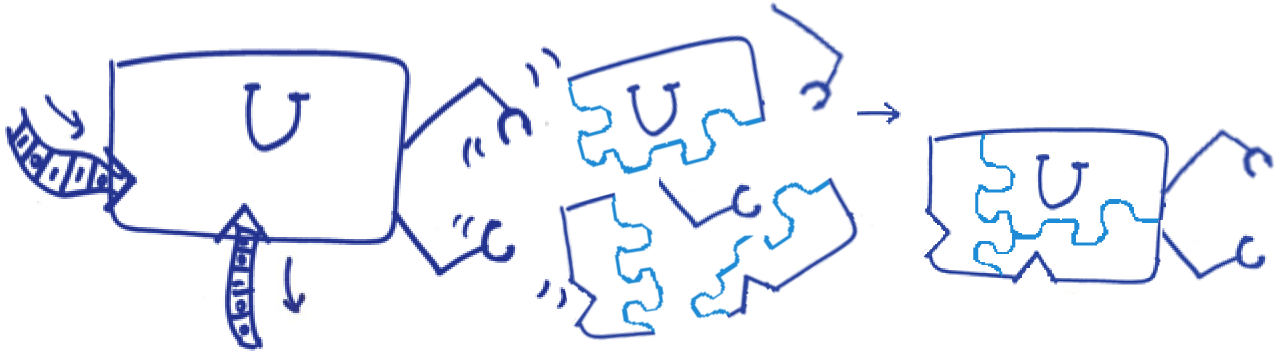
universal constructor

coded instructions



R machine (template replicate instructions)

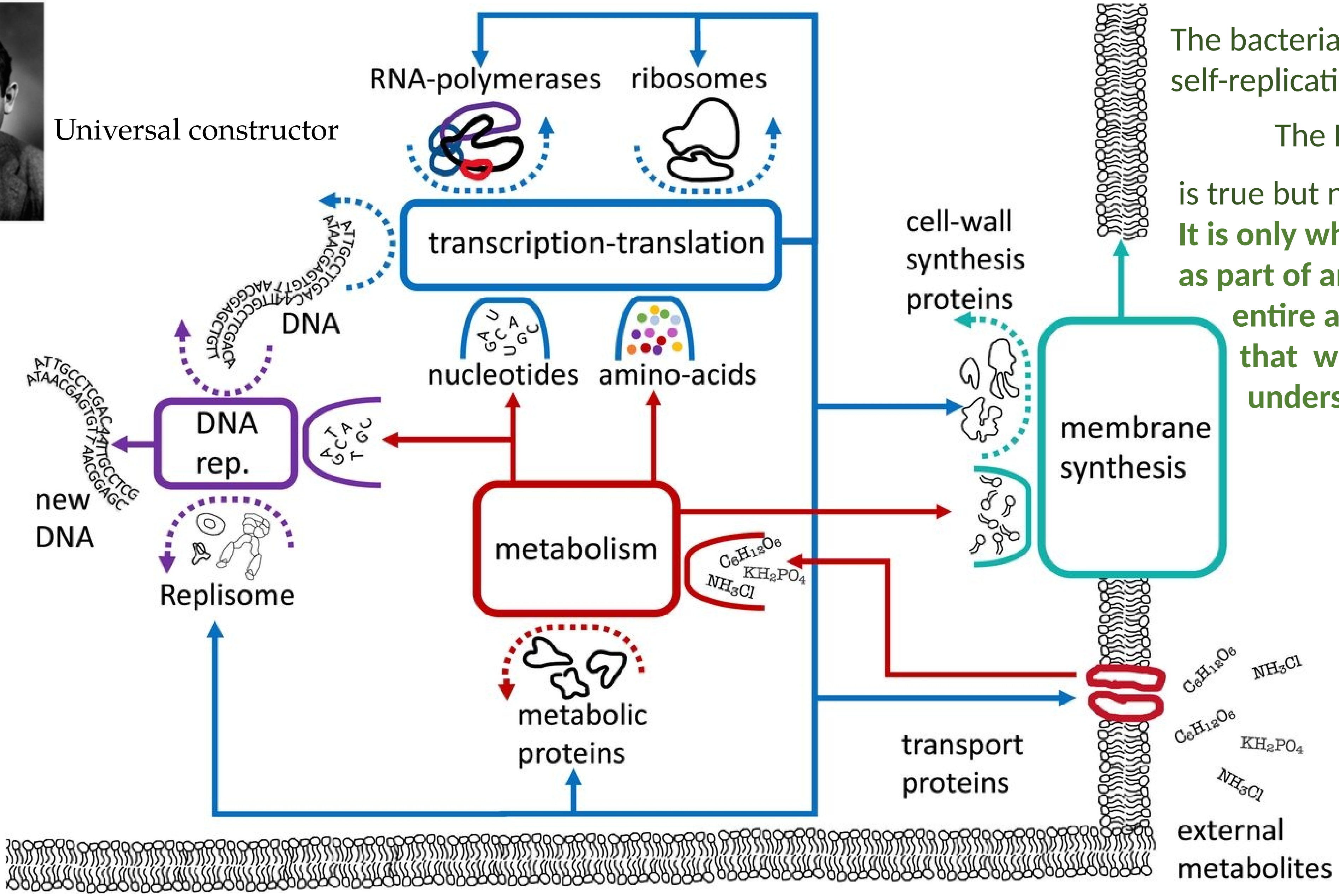
U can build itself



Universal constructor – the machine that makes machines

Schematic diagram of a bacterial autocatalytic network, showcasing different autocatalytic cycles coarsely grained.

Universal constructor



The bacterial cell as an ecology of self-replicating molecular machines

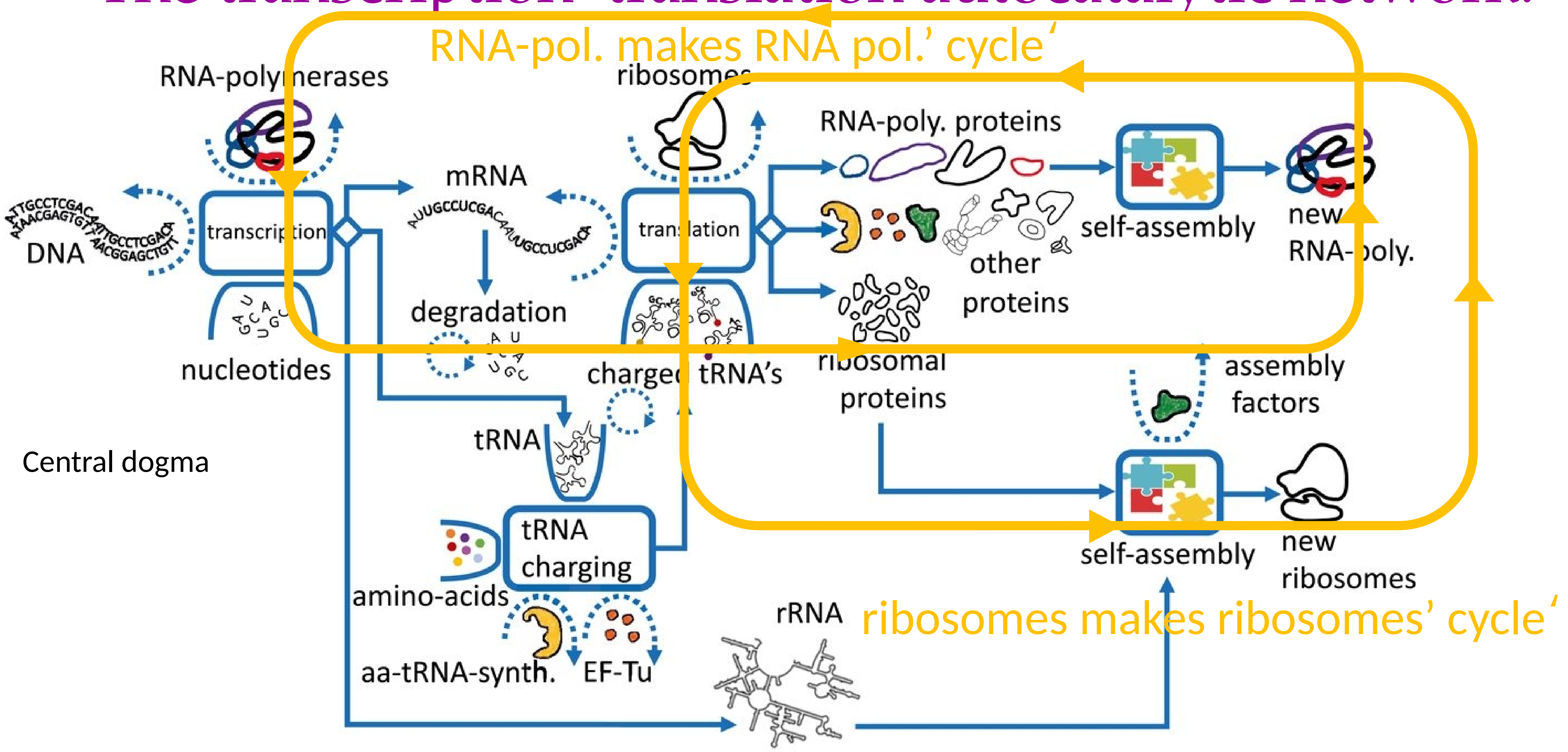
The Equation

is true but non-mechanistic

It is only when we view as part of an eigenvector of the entire autocatalytic network that we gain mechanistic understanding.

Anjan Roy et al. PNAS 2021 Vol. 118 No. 33 e2107829118.

The transcription–translation autocatalytic network.



Central dogma

Anjan Roy et al. PNAS 2021 Vol. 118 No. 33 e2107829118.

Our contribution

Using autocatalytic network with a specific structure that is common to all bacteria and using Leontif production function we derive

- Known growth laws

- New growth laws (in particular RNA-polymerase growth law)

- Employ RNAP growth law to explain reduction in growth rate at constant RNA/protein ratio as rifampicin concentration increases.

Autocatalysis 101 + a grapical language to code quantitiave models

- Simple reactions consume substrates $S_1,\ldots,S_n$, with a catalyst C and produce a product P

substrates reaction node de-novo synthesized product

catalyst

Wassily Leontief

Autocatalysis 101 cont.

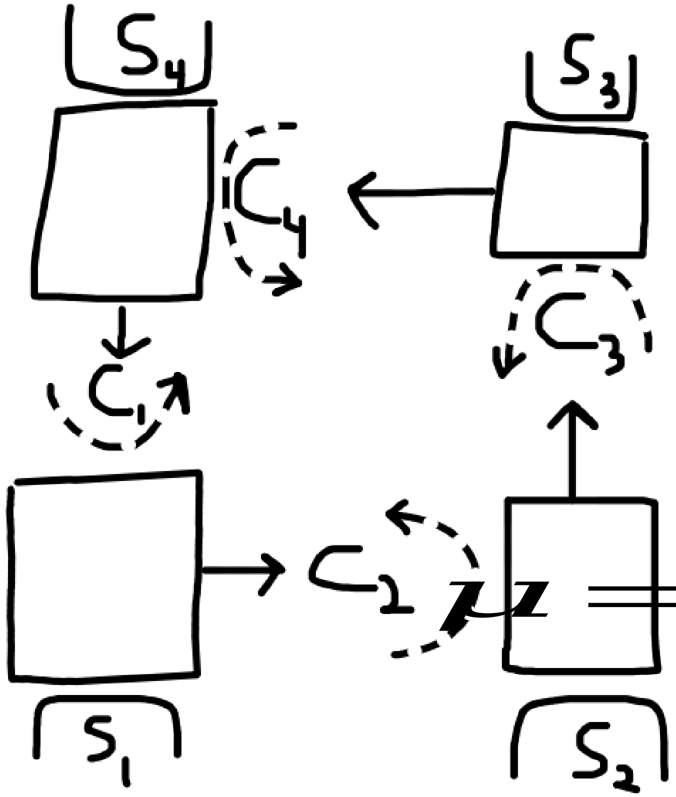
- Simple autocatalysis consume substrates $S_1,\ldots,S_n$, employ a catalyst C and the product is more catalysts C. The newly created catalysts joins the existing ones and catalyze more copies. This can go on until one of the substrates is depleted.

The product is another catalyst

Wassily Leontief

Autocatalytic networks

- networks which consume substrates and jointly autocatalyze all the catalysts in them. A famous (non biological) example is the Hinshelwood cycle (here of degree n=4):



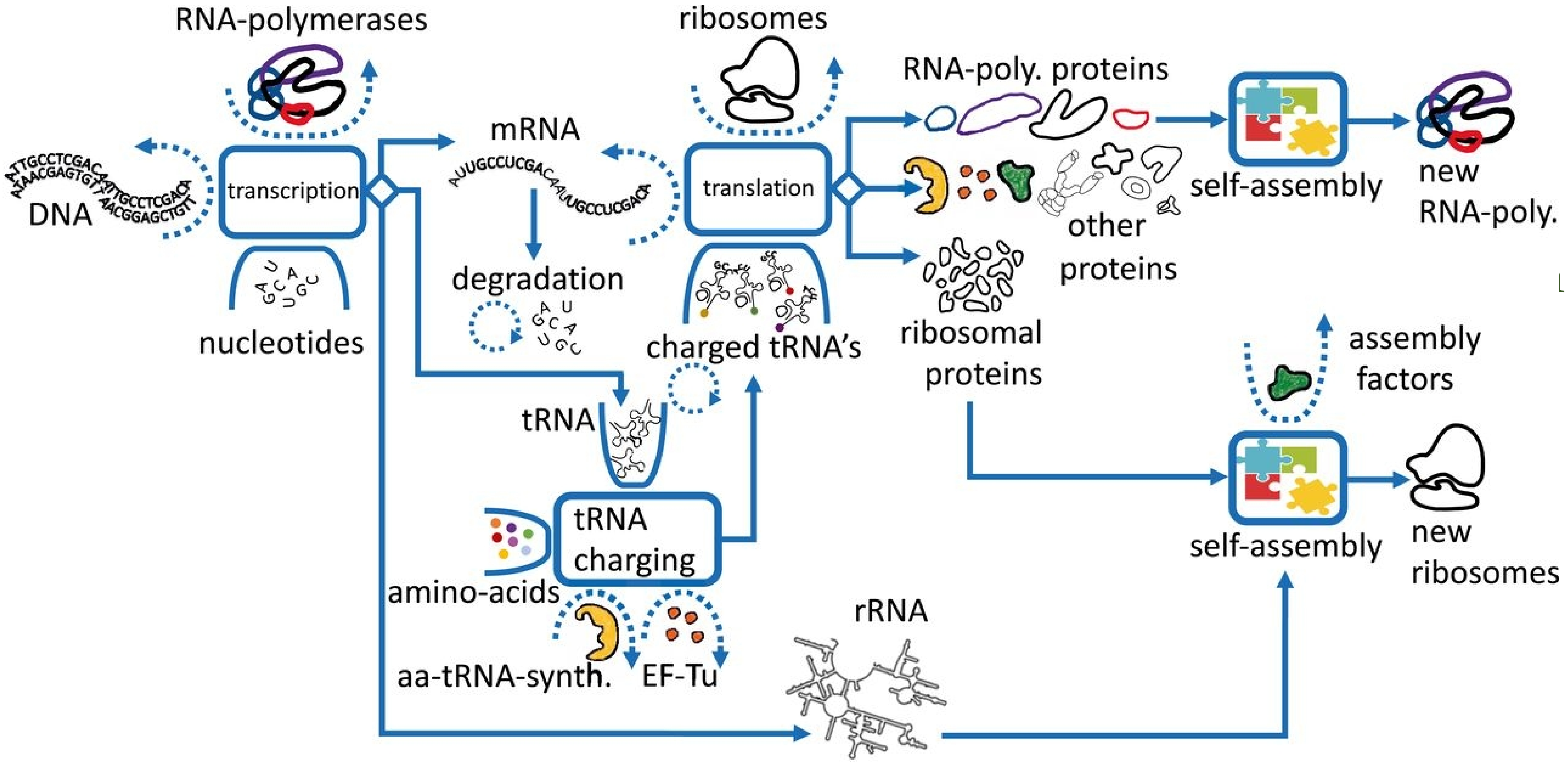
for example if all substrates are saturated

it is easy to show that

$$\mu = \frac{1}{\sqrt[n]{\tau_1 \times \tau_2 \times \ldots \times \tau_n}}$$

Cyril Hinshelwood

The graphical depiction of autocatalytic network codes a quantitative model



Going beyond the ribo-centric view

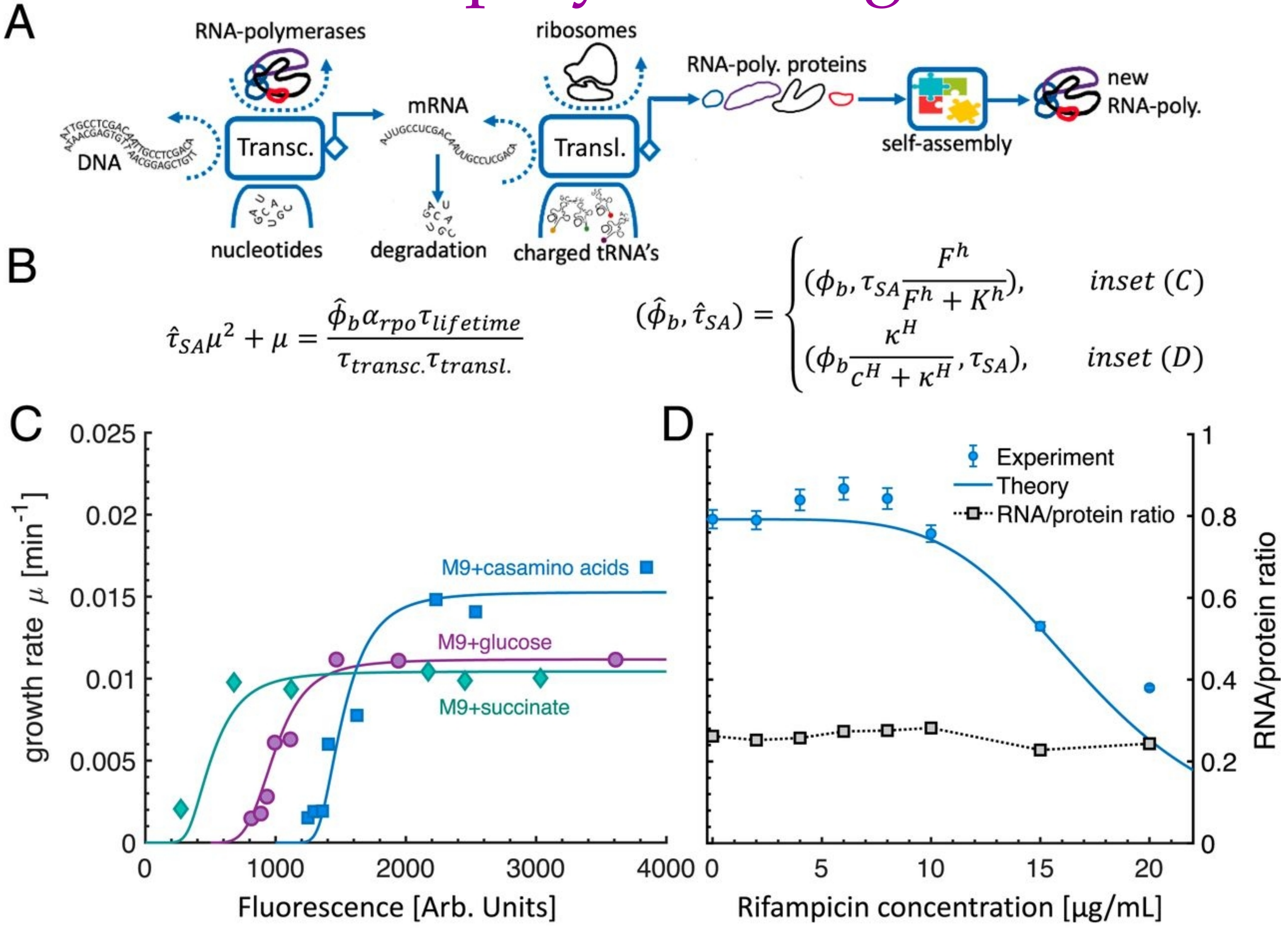
- In an autocatalytic network, any element can be viewd as the center around which autocatalysis revolves this leads to two growth laws per cycle.

  NOTE: <u>cycle need not be limiting</u>.

(i) a growth law involving all the time scales in the cycle (+allocation parameters).

(ii) a growth law involving relative abundance of a given catalyst, its synthesis rate and its allocation parameter (famous example: ribosome growth law).

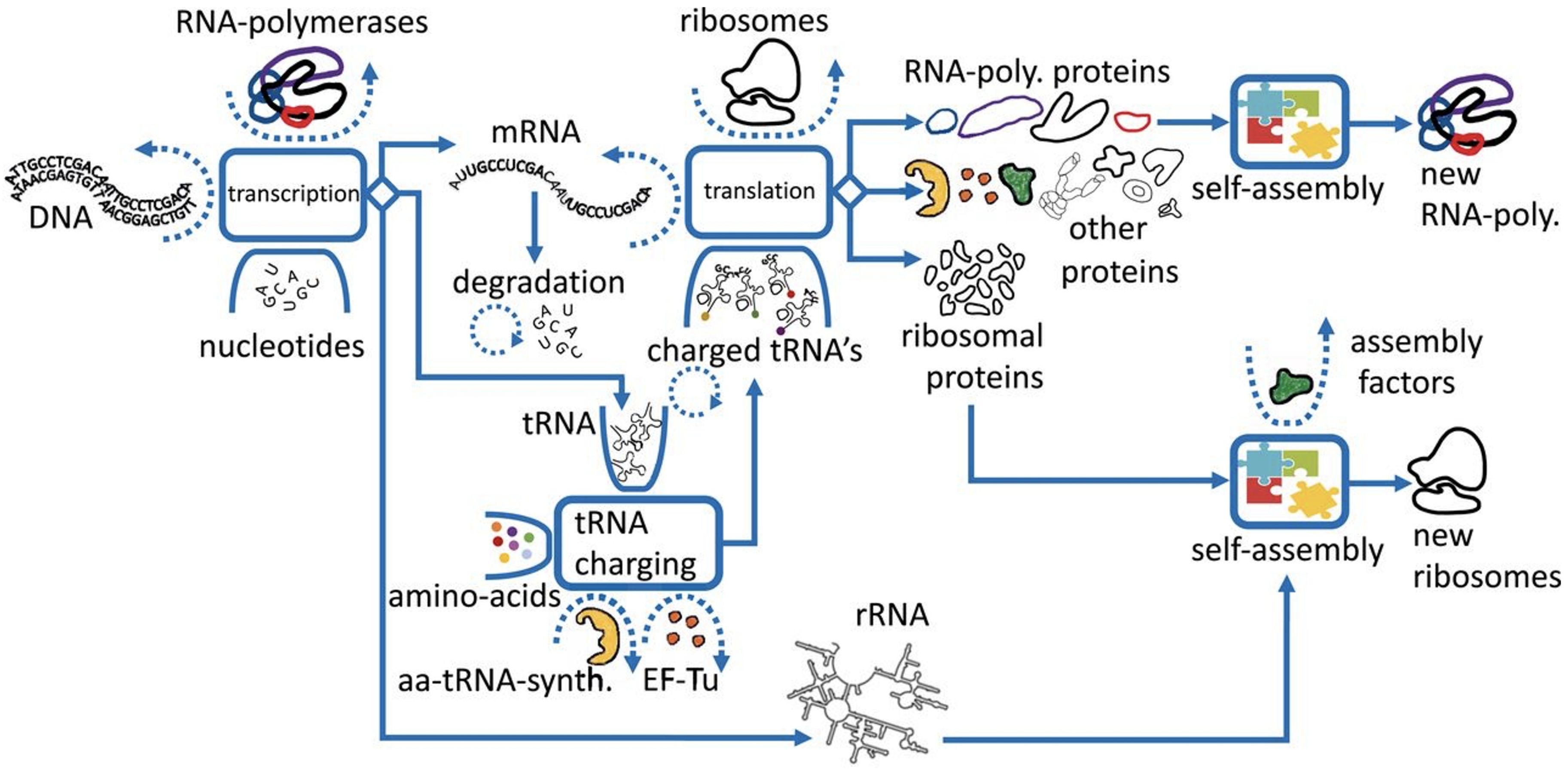
The RNA polymerase growth law

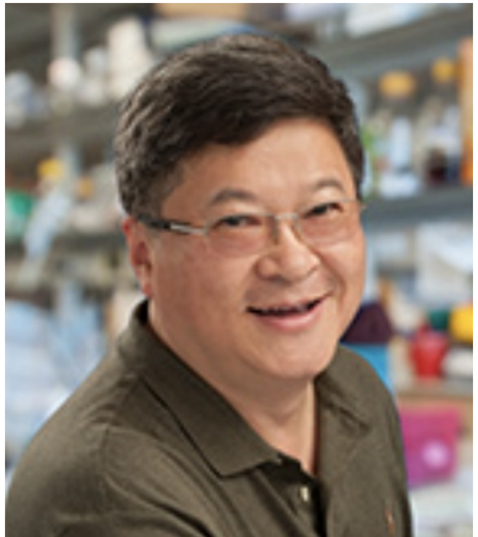


RNA/Protein = const.
yet growth rate goes down

Anjan Roy et al. PNAS 2021;118:33:e2107829118

Bacterial growth laws





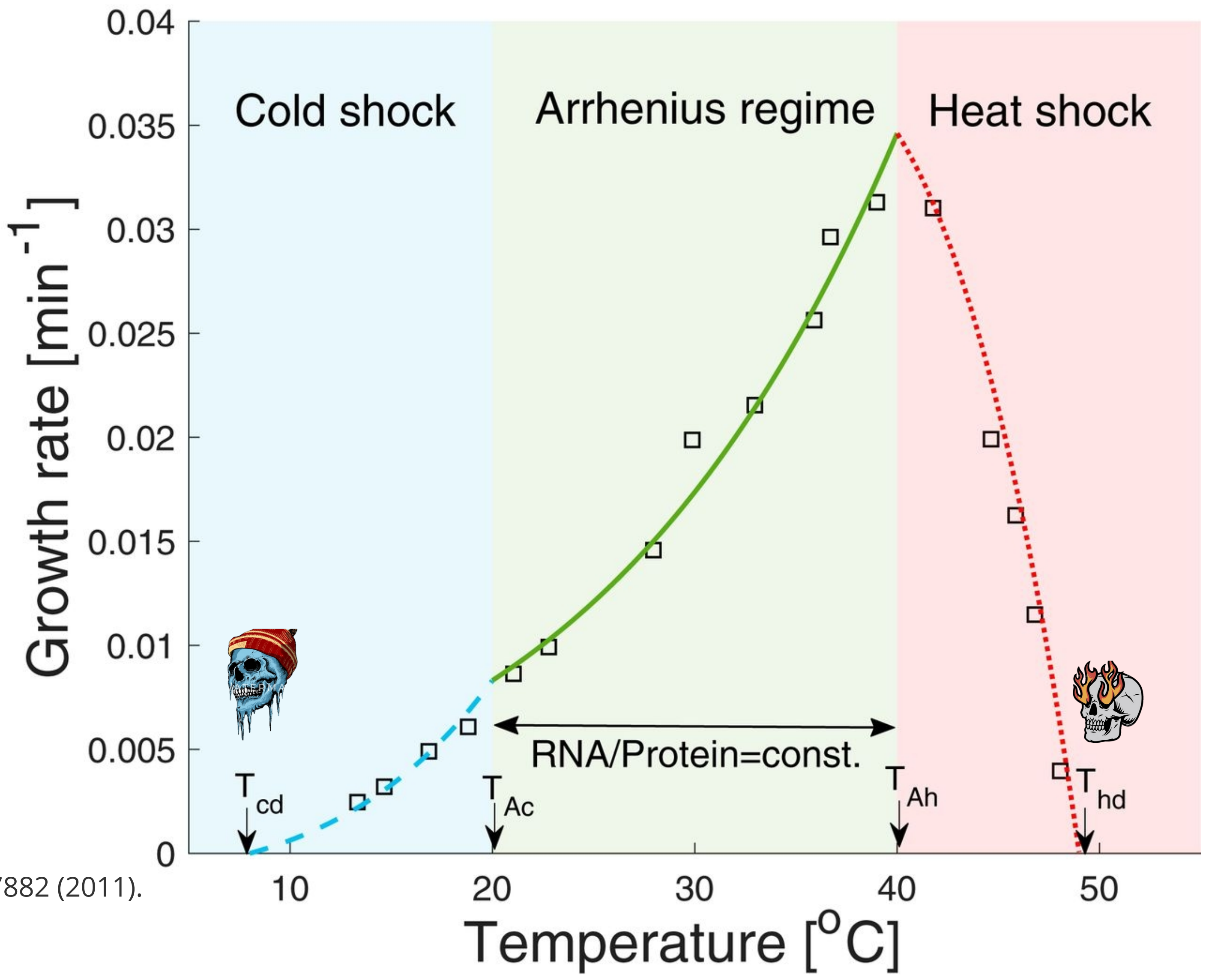
Growth rate dependence on temperature

$$\mu(T) = \gamma_{elong.} e^{\frac{\Delta\widetilde{G}}{k_B T}} \times \begin{cases} \Delta\Phi\frac{(T-T_{Ac})}{(T_{Ac}-T_{cd})} + \Delta\Phi, T < T_{Ac} \\ \Delta\Phi \qquad\qquad ,T \in [T_{Ac}, T_{Ah}] \\ \Delta\Phi\frac{(T-T_{Ah})}{(T_{Ah}-T_{hd})} + \Delta\Phi, T > T_{Ah}, \end{cases}$$

$$\Delta G(T) = \Delta H + \Delta C_p \left(T - \hat{T}\right) - T\Delta S - T\Delta\, C_p \ln\left(\frac{T}{385}\right),$$

$$\Delta\widetilde{G} = \Delta G - \Delta G(T = 37^o C)$$

K. A. Dill, K. Ghosh, J. D. Schmit, Proc. Natl. Acad. Sci. U.S.A. **108**, 17876–17882 (2011).



Anjan Roy et al. PNAS 2021;118:33:e2107829118

Two-step model buildup.

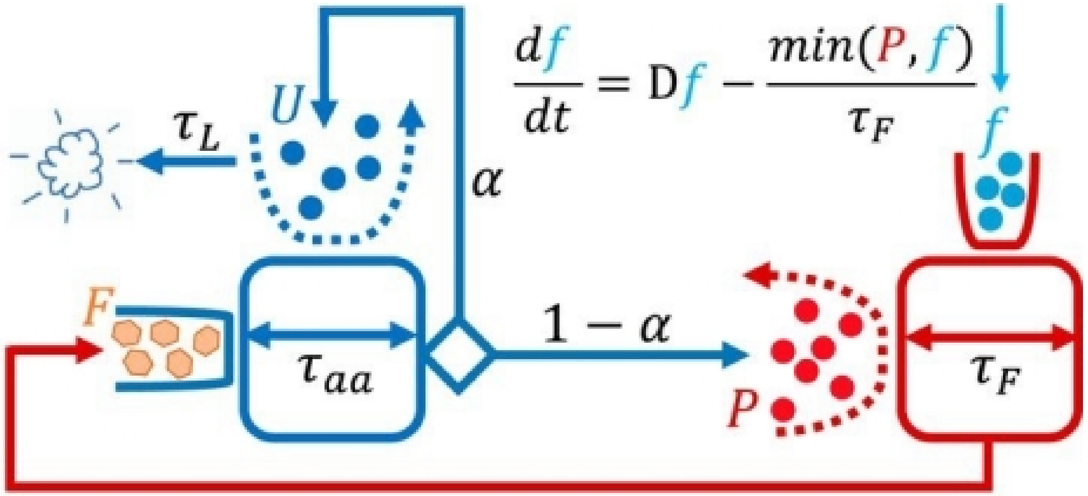
A

$$\frac{dU}{dt} = \frac{\alpha\, min(U, F)}{F_U \tau_{aa}} - \frac{U}{\tau_L}$$

$$\frac{dP}{dt} = \frac{(1-\alpha) min(U, F)}{F_P \tau_{aa}}$$

$$\frac{dF}{dt} = \frac{min(P, f)}{\tau_F} - \frac{min(U, F)}{\tau_{aa}}$$

$$\frac{df}{dt} = \mathrm{D} f - \frac{min(P, f)}{\tau_F}$$



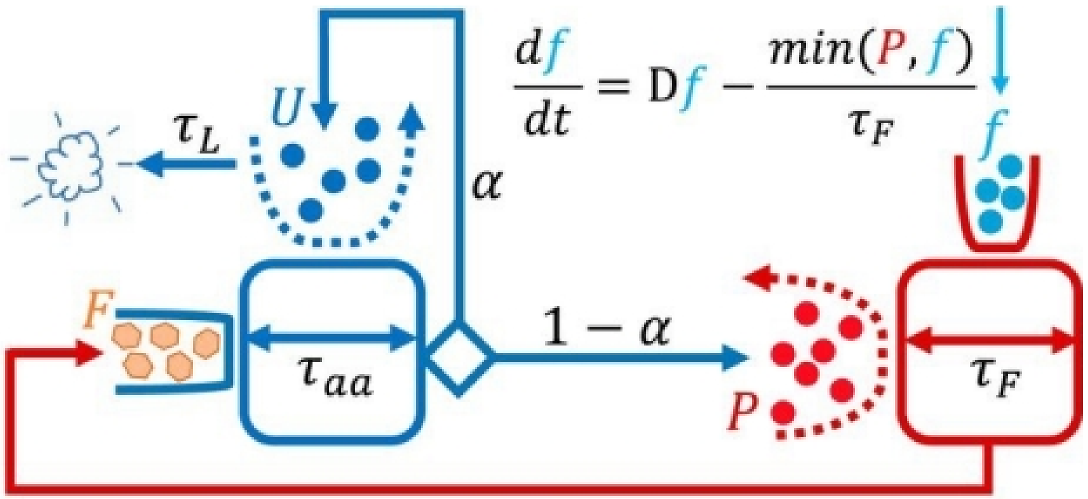
Two-step model buildup.

A

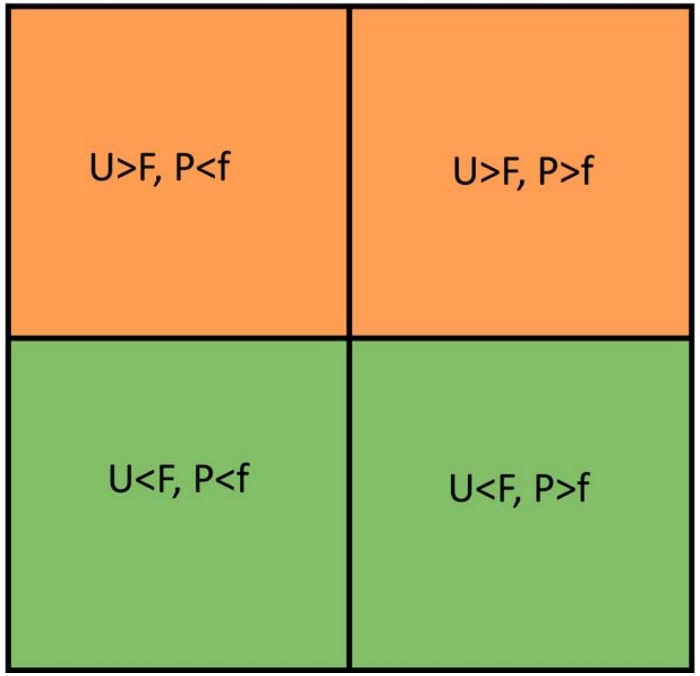
$$\frac{dU}{dt} = \frac{\alpha\, min(U,F)}{F_U \tau_{aa}} - \frac{U}{\tau_L}$$

$$\frac{dP}{dt} = \frac{(1-\alpha) min(U,F)}{F_P \tau_{aa}}$$

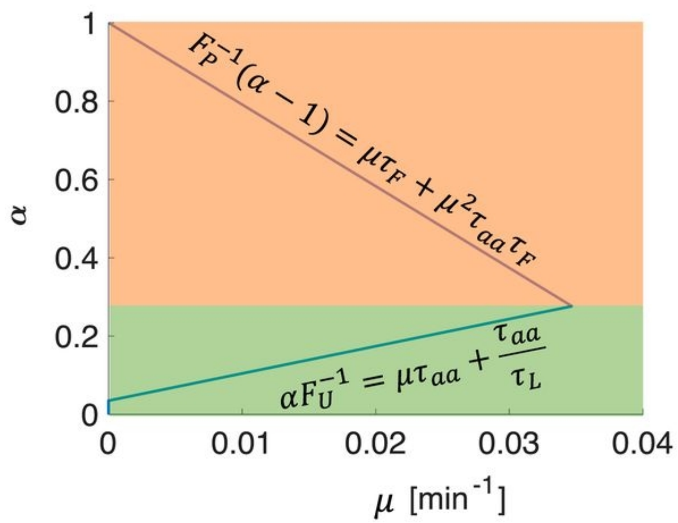
$$\frac{dF}{dt} = \frac{min(P,f)}{\tau_F} - \frac{min(U,F)}{\tau_{aa}}$$



A

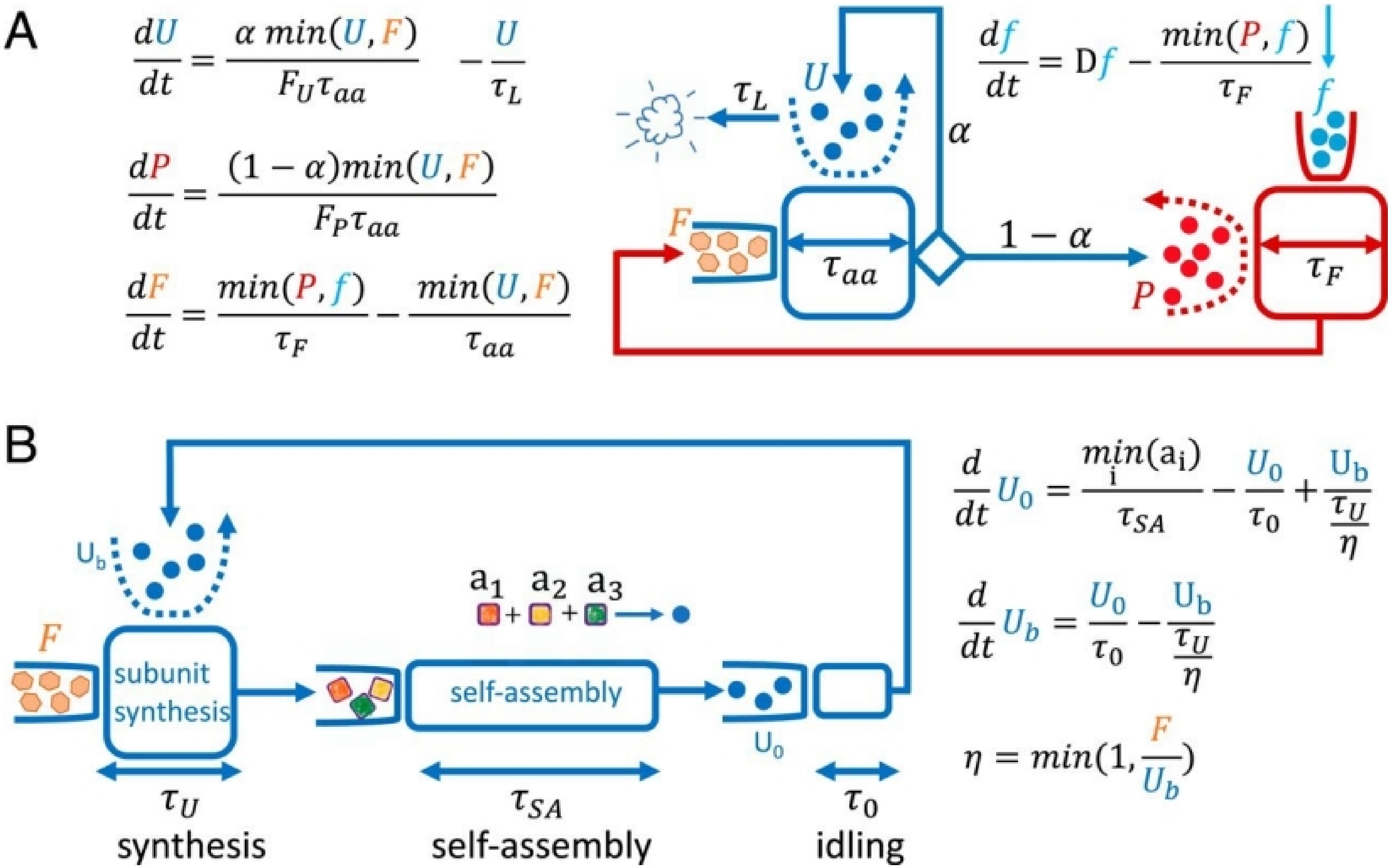


B

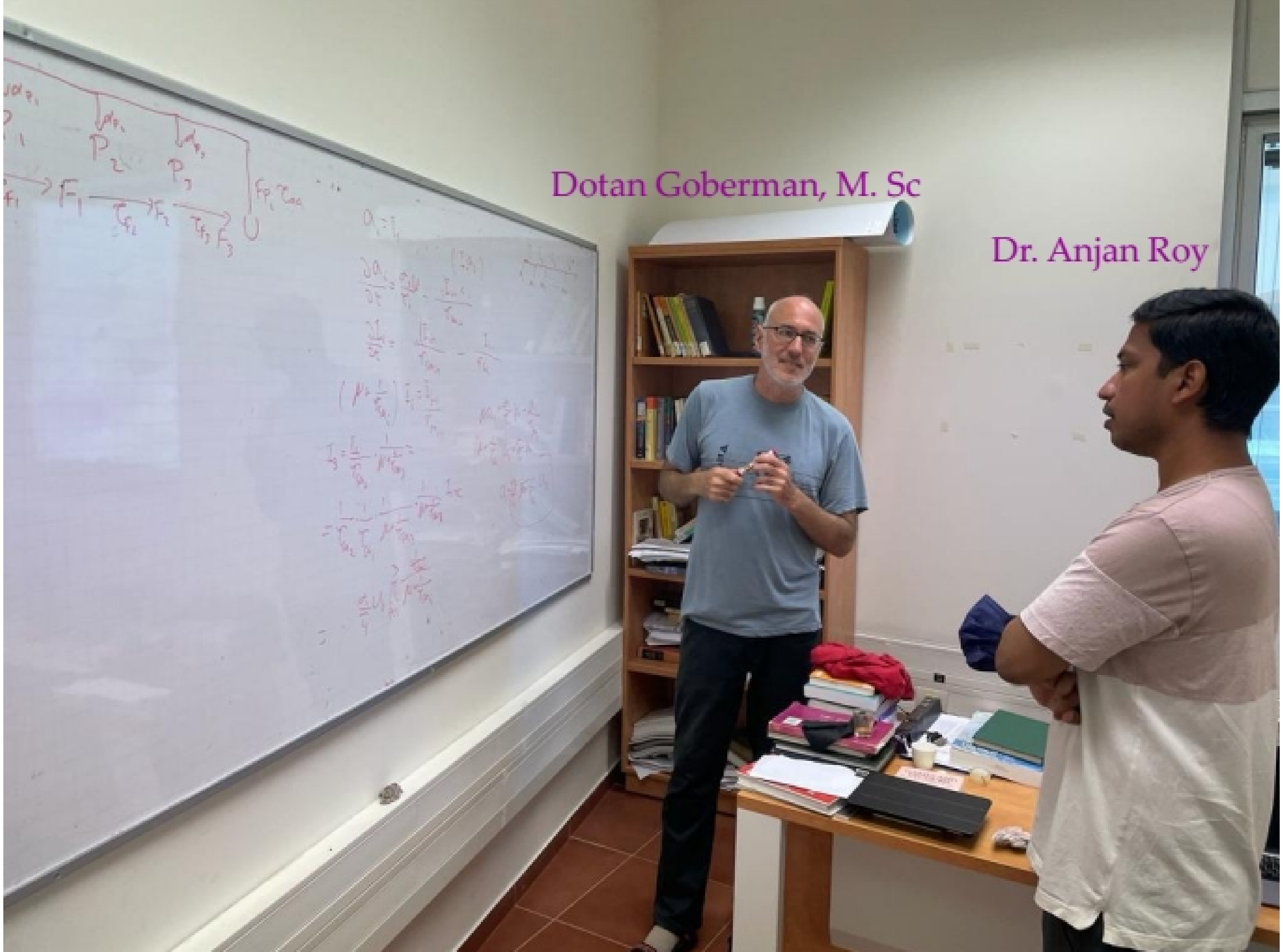


Anjan Roy et al. PNAS 2021;118:33:e2107829118

Two-step model buildup.



Anjan Roy et al. PNAS 2021;118:33:e2107829118

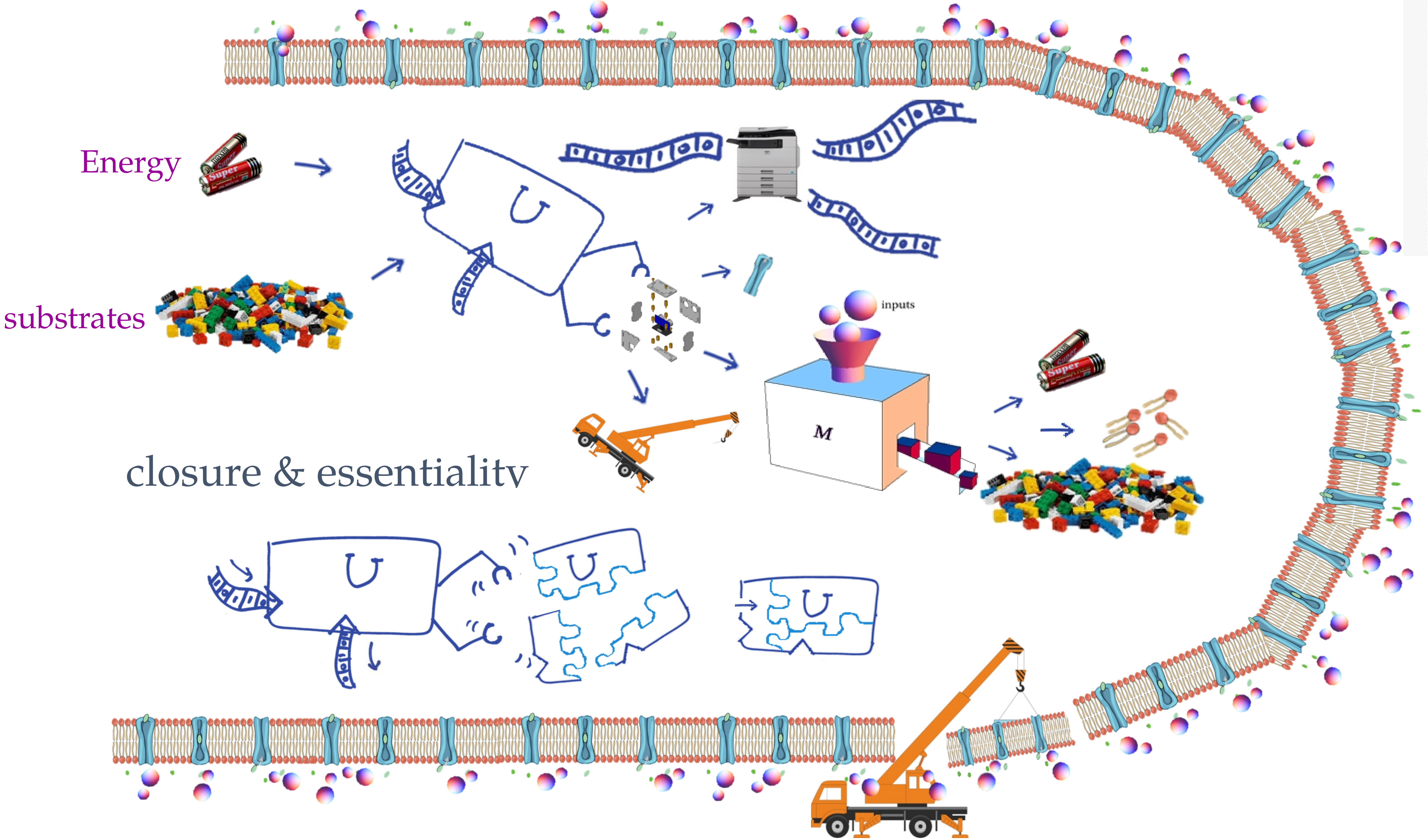

Dotan Goberman, M. Sc
Dr. Anjan Roy

What's next?

- Design rules for streamlining ribosome assembly
- Control in general and metabolic switchings
- Classification and analysis of all cost-benefit scenarios

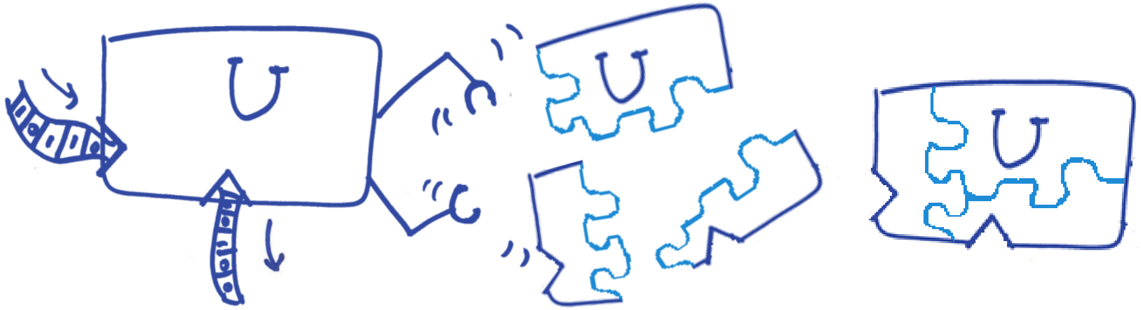
"All model are wrong,
some are useful."
G. Box

The Non-trivial Self-replicating Factory

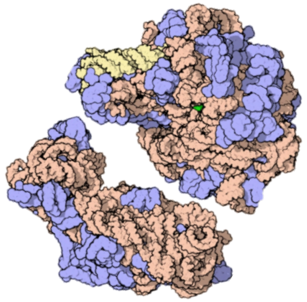


John von Neumann

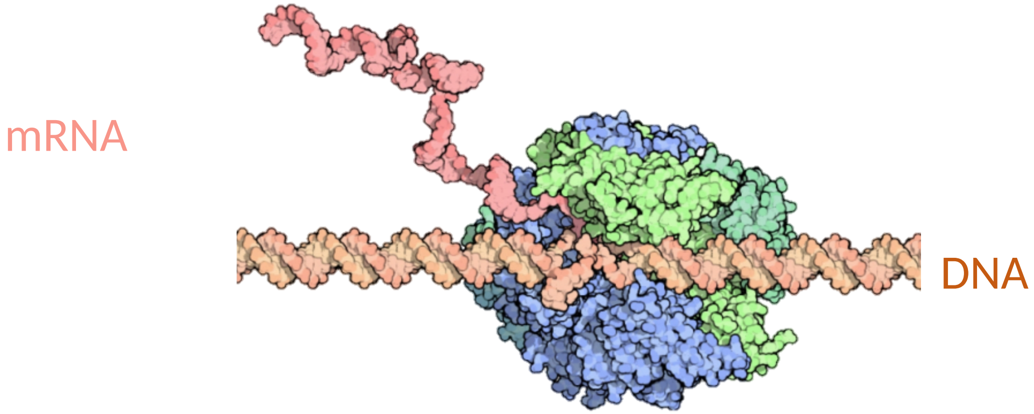
Who's the universal constructor in the cell?

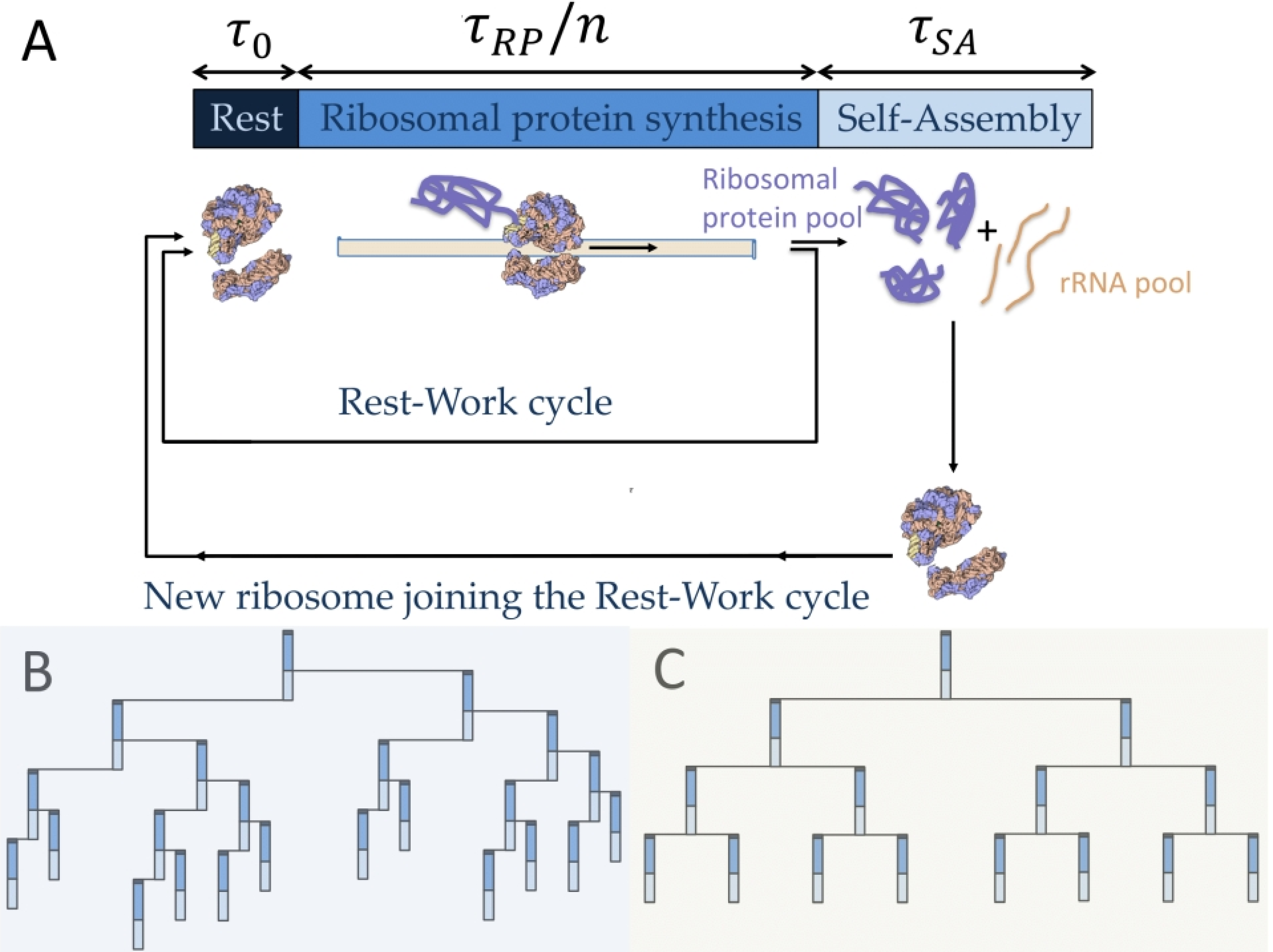


key players : RNA polymerase

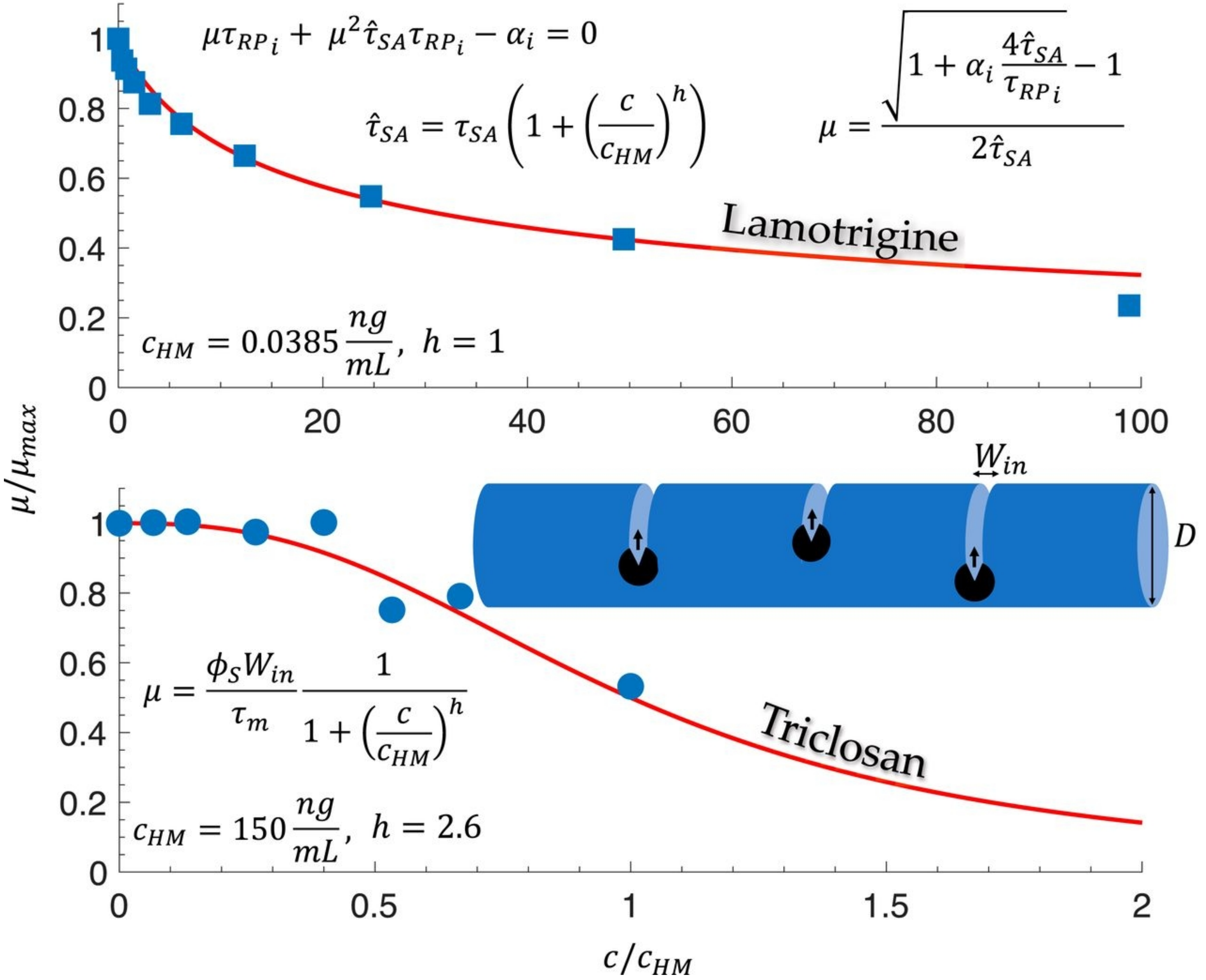


Ribosome




A
τ0
τRP/n
τSA
Rest
Ribosomal protein synthesis
Self-Assembly
Ribosomal
protein pool
+
rRNA pool
Rest-Work cycle
New ribosome joining the Rest-Work cycle
B
C

Effect of two antibacterial agents—lamotrigine and triclosan—on E. coli



Q: What about noise?

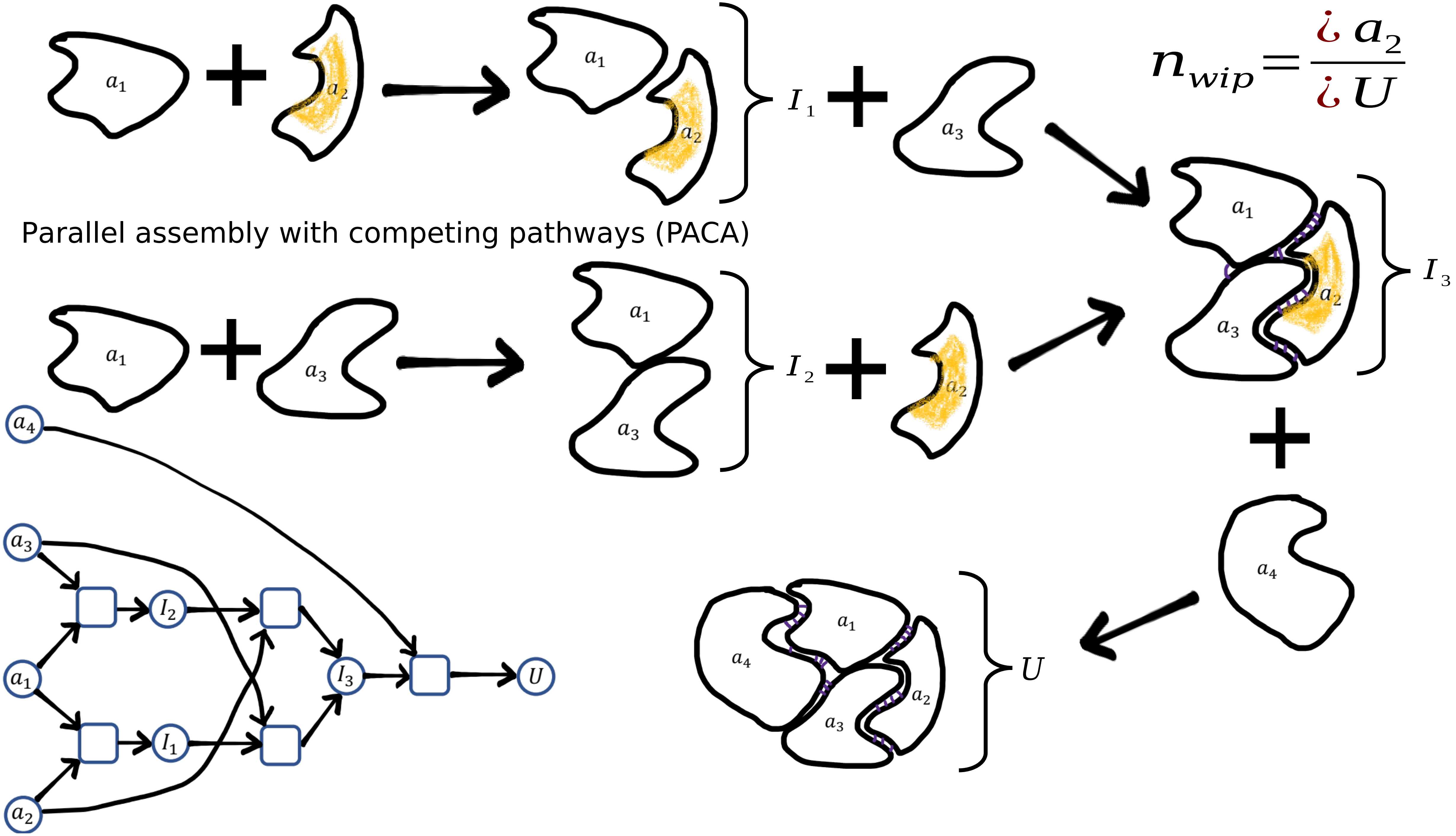
A: Surprisingly unimportant

Approximate growth law: Little's law for self-replicating factories

$$\mu \approx \frac{\left(1-\sqrt{1-cv^2 n_{WIP}}\right)}{\tau_{SA}\frac{cv^2}{2}} \approx \frac{n_{WIP}}{\tau_{SA}}$$

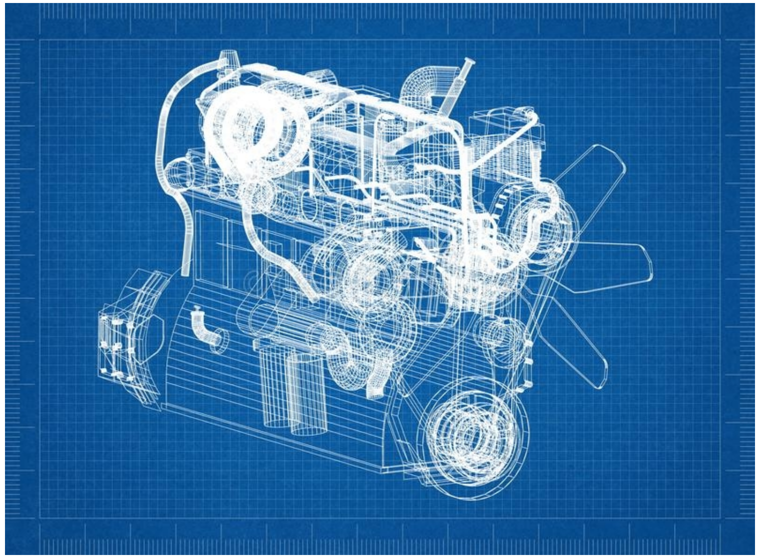
2nd order (cv = coefficient of variation)

1st order (n_{WIP} =relative work in process – percentage)

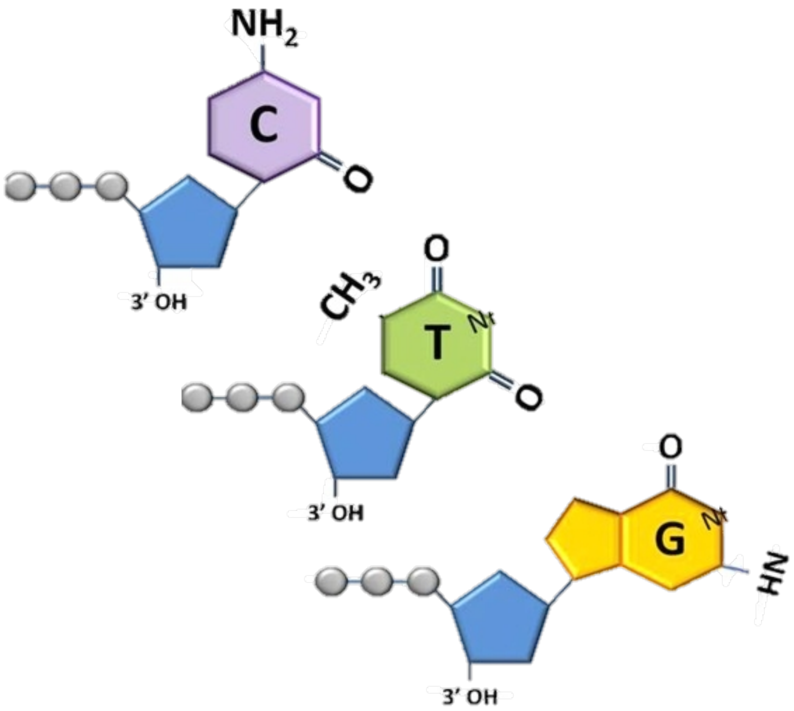

Parallel assembly with competing pathways (PACA)
$n_{wip} = \frac{¿\, a_2}{¿\, U}$
a_1
a_2
a_3
a_4
I_1
I_2
I_3
U

Coolant Leakage due to a hole in the radiator

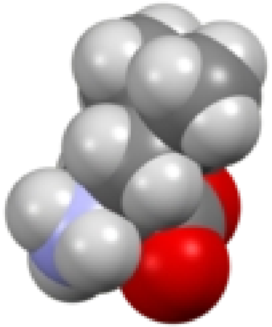
Inspecting engine blueprints will not reveal the cause unless malfunction is due to an inherent design flaw



The genetic code



CTG



Leucine

"Laplace transform of assembly time evaluated at s = growth rate = 1/(1+relative WIP)"

$$P_{SA}(\mu) = \frac{1}{1 + n_{WIP}}$$

Distribution	Laplace transform	Growth rate	Relative WIP
Deterministic	$e^{-\mu\tau_{SA}}$	$\mu = \frac{1}{\tau_{SA}}\ln(1 + n_{WIP})$	$n_{WIP} = e^{\mu\tau_{SA}} - 1$
Exponential	$\frac{1}{1 + \mu\tau_{SA}}$	$\mu = \frac{n_{WIP}}{\tau_{SA}}$	$n_{WIP} = \mu\tau_{SA}$
Erlang –k	$\frac{1}{\left(1 + \frac{\mu\tau_{SA}}{k}\right)^k}$	$\mu = \frac{k}{\tau_{SA}}\left(\sqrt[k]{1 + n_{WIP}} - 1\right)$	$n_{WIP} = \left(1 + \frac{\mu\tau_{SA}}{k}\right)^k - 1$
Mixture of two exponentials	$\frac{p\lambda_1}{\lambda_1 + \mu} + \frac{(1-p)\lambda_2}{\lambda_2 + \mu}$	Numerical	Numerical
Shifted exponential	$\frac{e^{-\mu\tau}}{1 + \frac{\mu}{\lambda}}$	$\mu = \frac{\mathcal{L}_w\lambda\left(\tau e^{\lambda\tau}(1 + n_{WIP})\right)}{\tau} - \lambda$	$n_{WIP} = e^{\mu\tau}\left(1 + \frac{\mu}{\lambda}\right) - 1$