



Traffic jam generates phase transition in translation

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<http://www.abdn.ac.uk/icsmb/people/details/grebogi>

Queueing phase transition: theory of translation, M. C. Romano, M. Thiel, I. Stansfield, and C. Grebogi, Phys. Rev. Lett. **102**, 198104 (2009)

Limited resources in a driven diffusion process, C. A. Brackley, M. C. Romano, C. Grebogi, and M. Thiel, Phys. Rev. Lett. **105** 078102 (2010)

Community Control in the Cellular Protein Production: Consequences for Amino Acid Starvation, F. Heldt, C. A. Brackley, C. Grebogi and M. Thiel, in print.

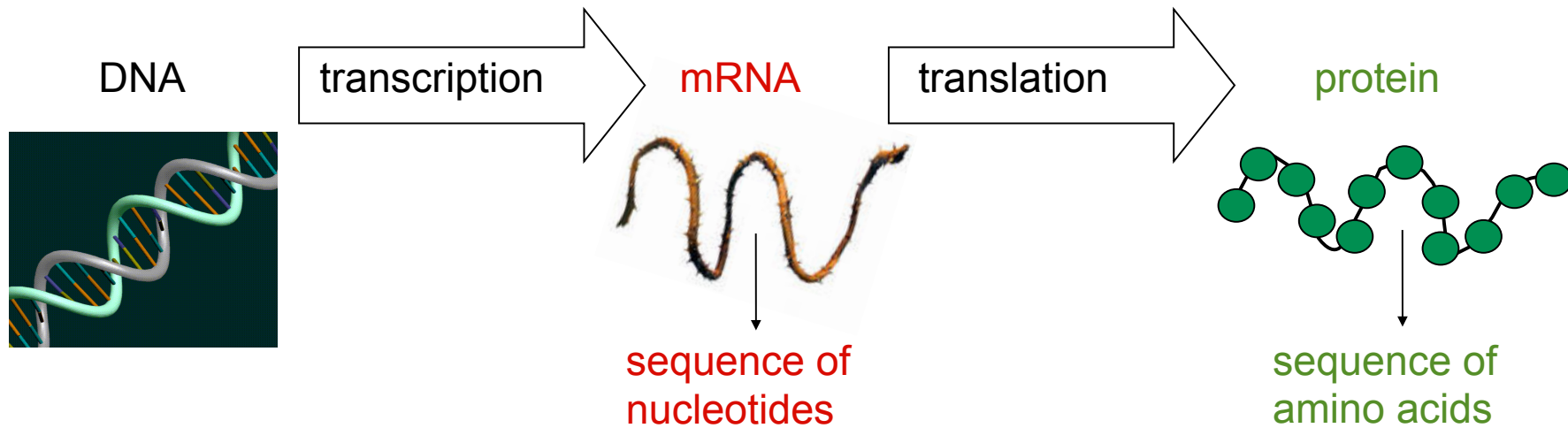


Outline

- The biological process of translation.
- Relationship between traffic dynamics and biological function of proteins.
- Limited resources regime
- Concluding remarks.



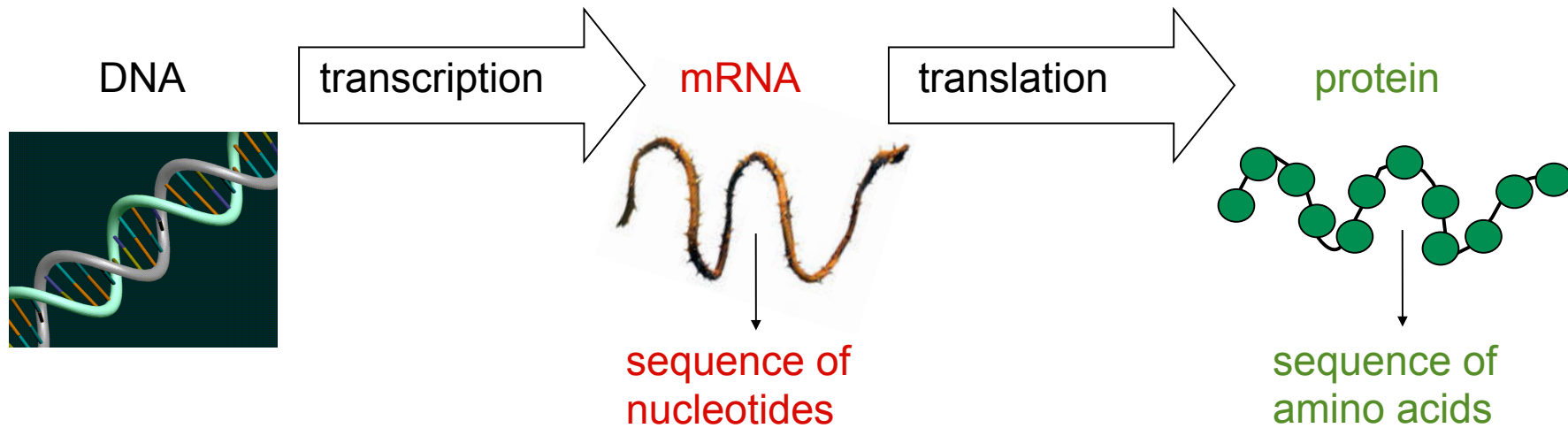
The central dogma of biology



- 4 different nucleotides: **A, C, G, U**
- 20 different amino acids: **Alanine, Glutamine, Histidine, ...**



The central dogma of biology



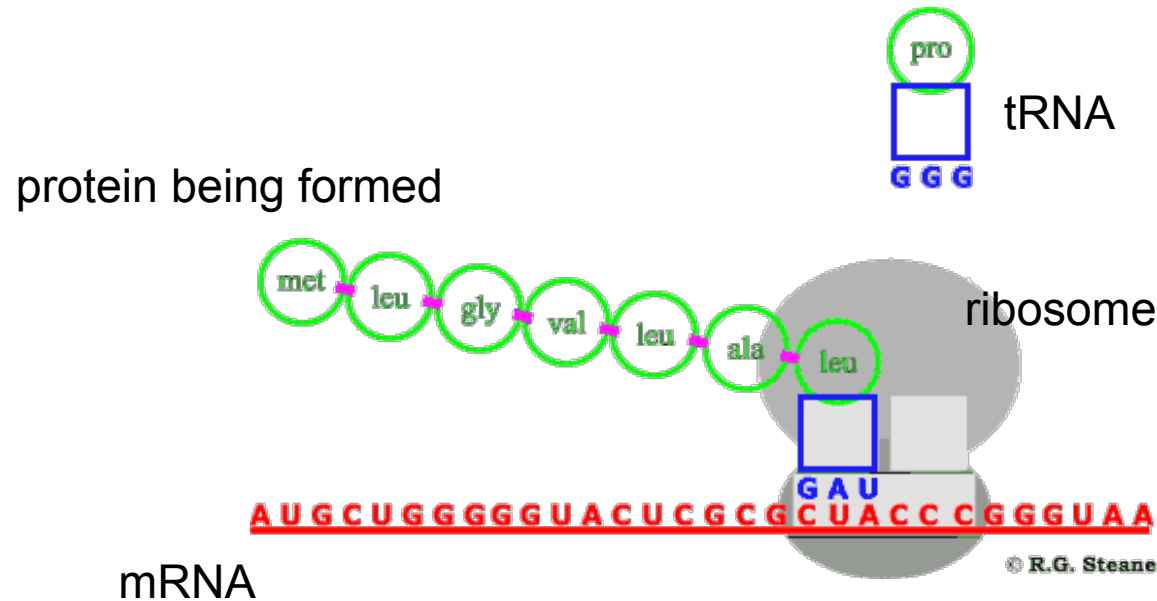
- 4 different nucleotides: **A, C, G, U**
- 20 different amino acids: **Alanine, Glutamine, Histidine, ...**
- **3 consecutive nucleotides (CODON) → 1 amino acid**

64 different codons, some of which are synonymous

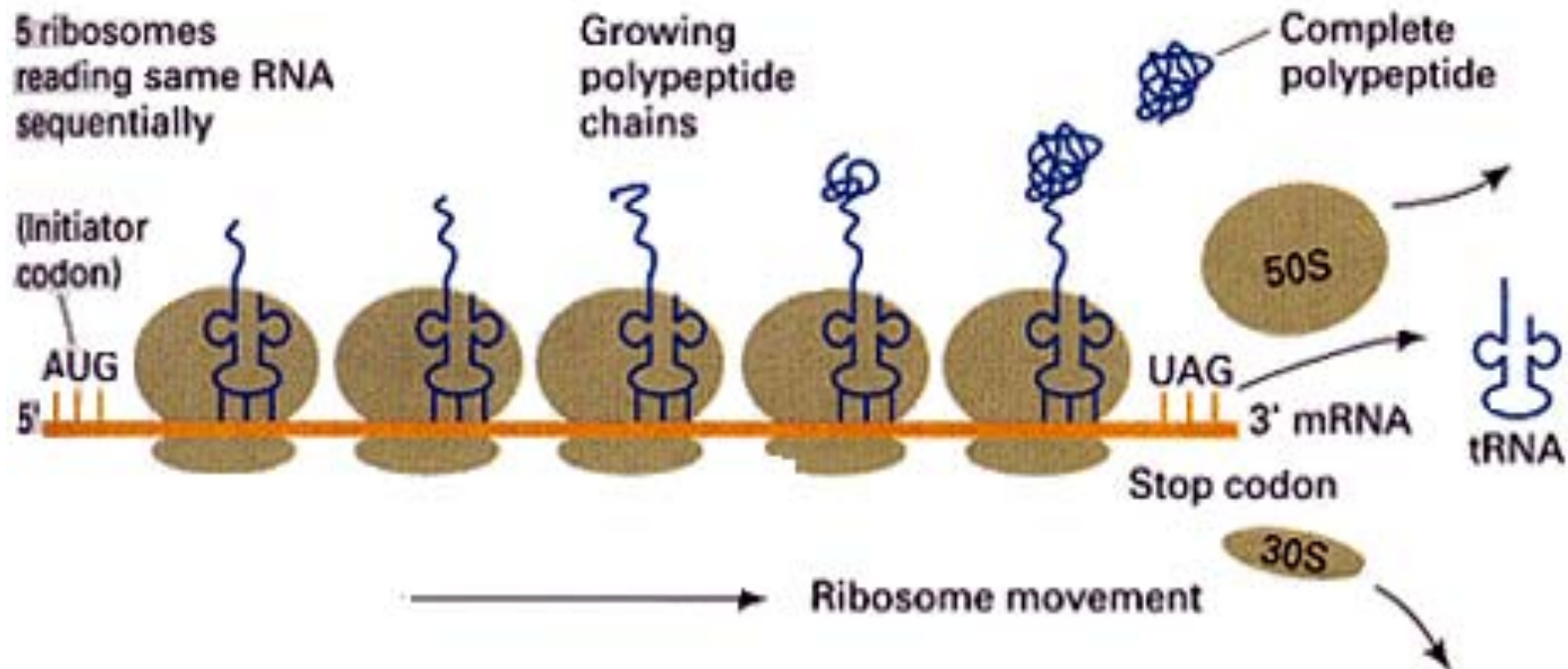
(e.g., Alanine is encoded by: GCU, GCC, GCA, GCG)



Translation is performed by ribosomes



- At each codon the ribosome has to wait for the **tRNA** which carries the corresponding **anticodon** and apports the right amino acid to the growing polypeptide chain.
- There are **41 different types of tRNAs** in yeast. All of them are present in the cytoplasm but at a different concentration.





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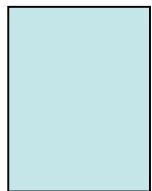
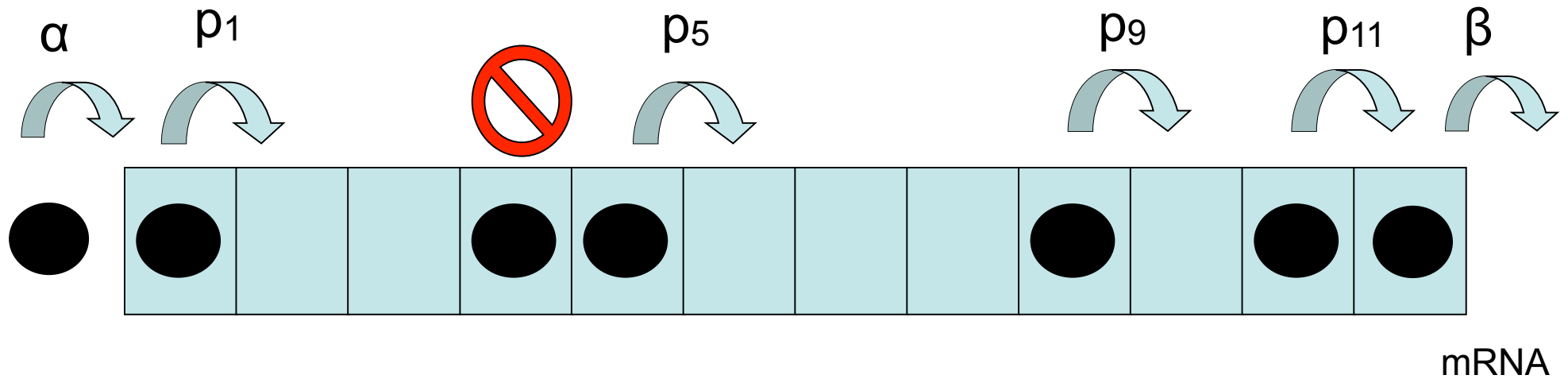


Experimental findings

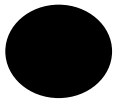
- *Replacement of rare codons by common ones increases the production rate of proteins.*
- *It is possible to increase the production rate of proteins by modulating the binding of tRNA with mRNA (e.g. with enzymes such as Trm9).*

How does the configuration of rare codons affect the flow of the ribosomes (translation rate) on the mRNA?

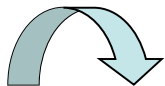
Stochastic Model of Translation



Codons occupied by one ribosome



Ribosome



The ribosome makes one step ahead with probability p_i



The ribosome is not allowed to make one step ahead because the next codon is occupied.



General case:
codons are different; open boundary conditions

$$u_i = p_i P_{i,i+1}(\bullet, \circ) + p_i P_{i,i+1}(\bullet, \bullet) u_{i+1|i}$$



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mean-field approximation

$$u_i = p_i(1 - \rho_{i+1}) + p_i \rho_{i+1} u_{i+1}$$



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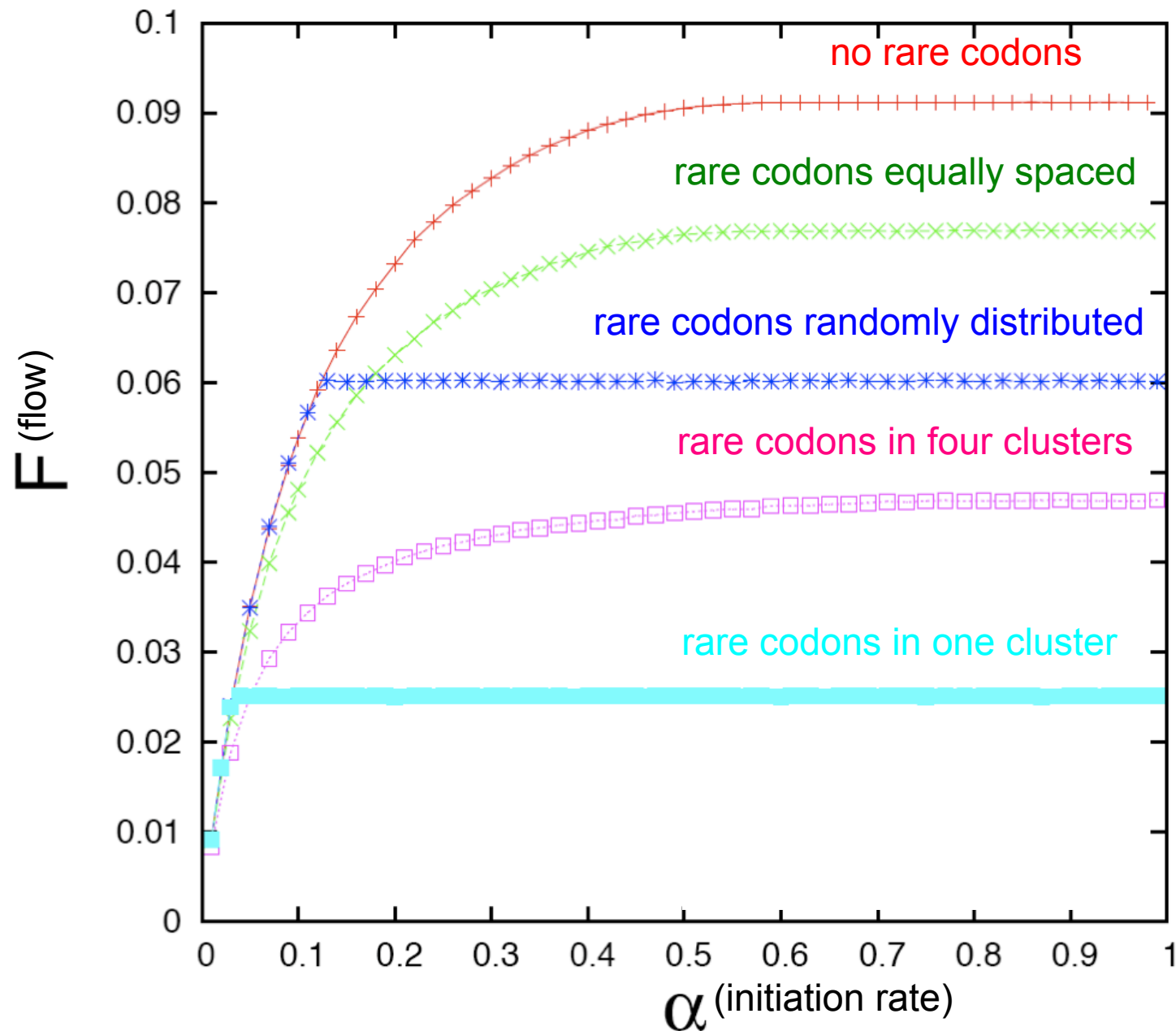
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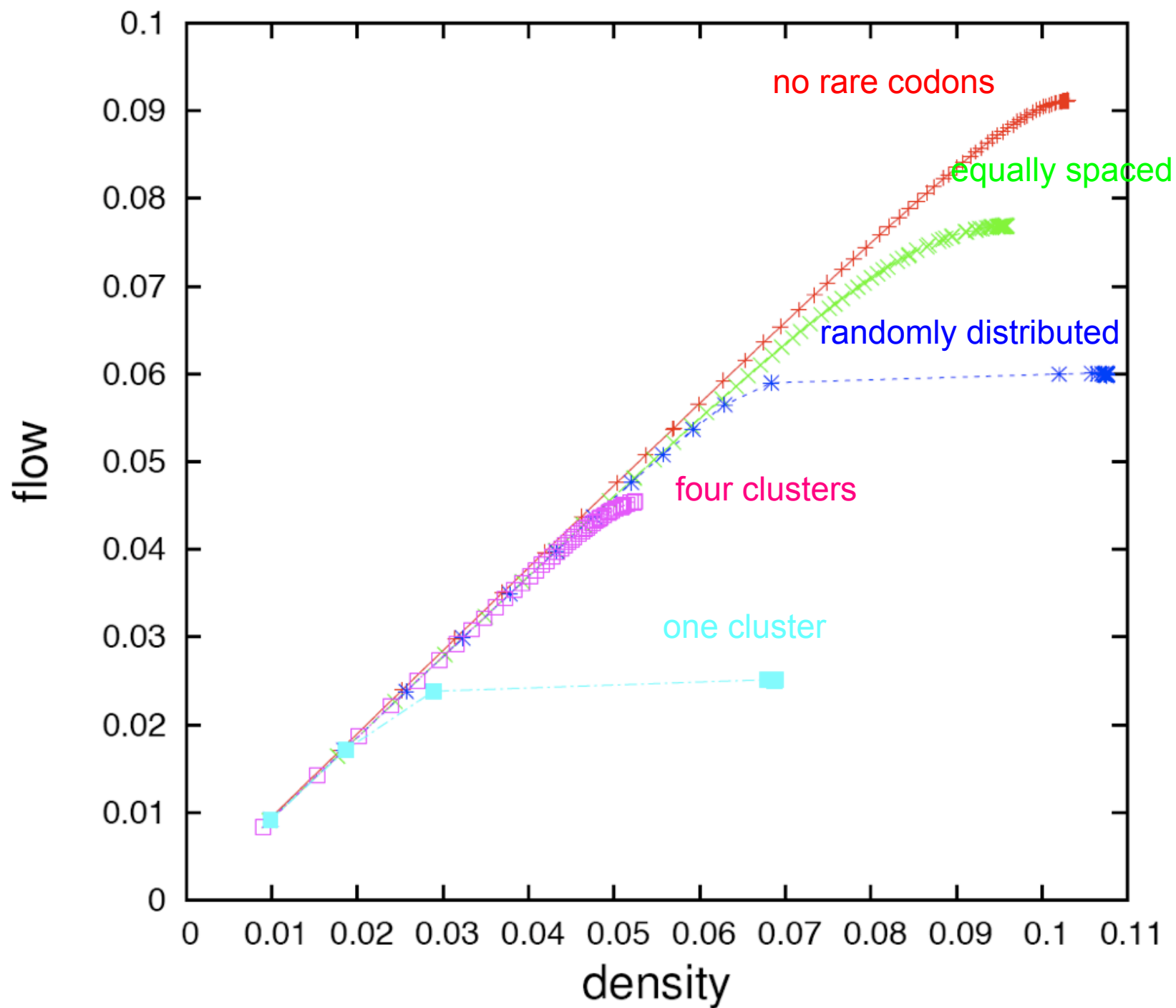
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How does the configuration of rare codons affect the flow of the ribosomes (translation rate) on the mRNA?



Monte-Carlo simulations: inhomogeneous lattice and realistic width of ribosomes

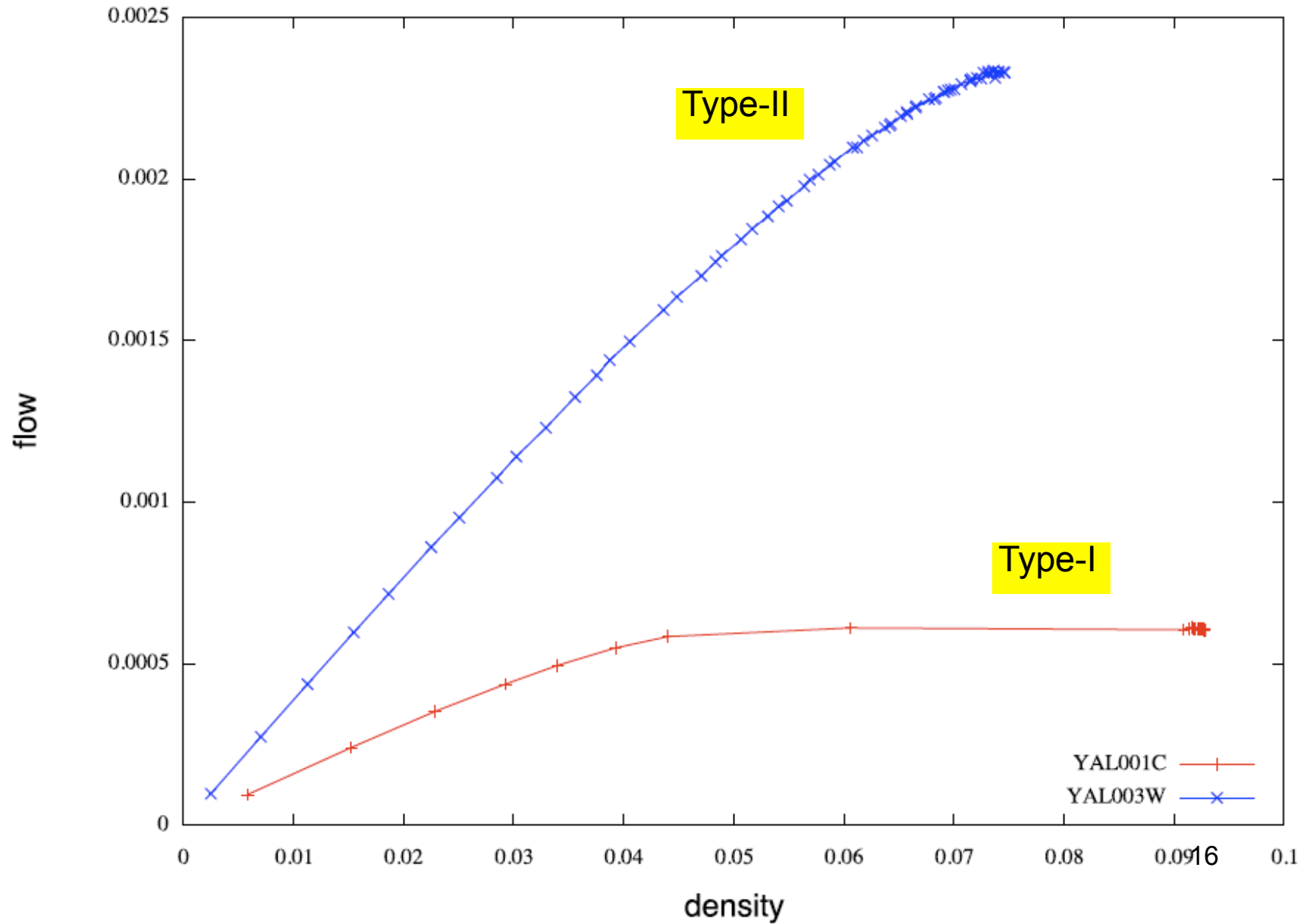






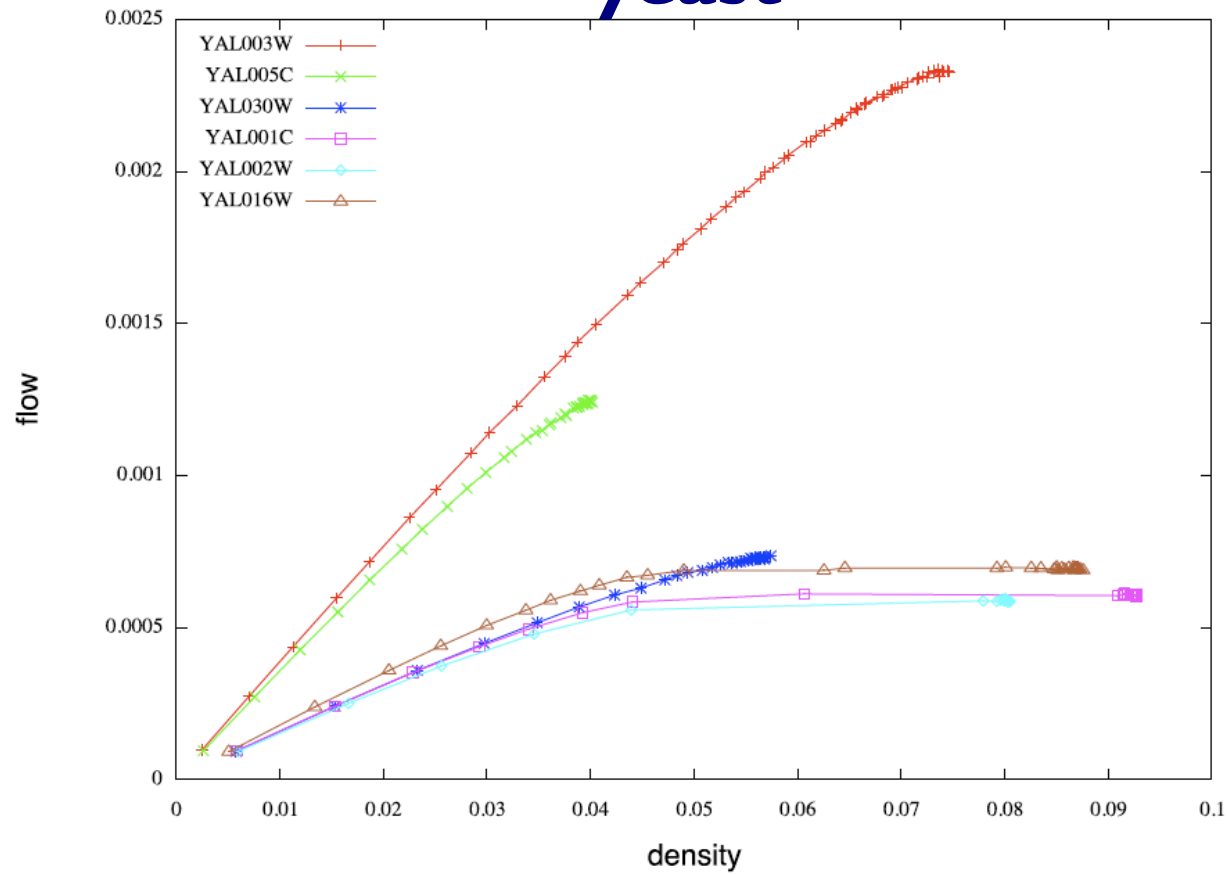
Real proteins:

YAL001C and YAL003W



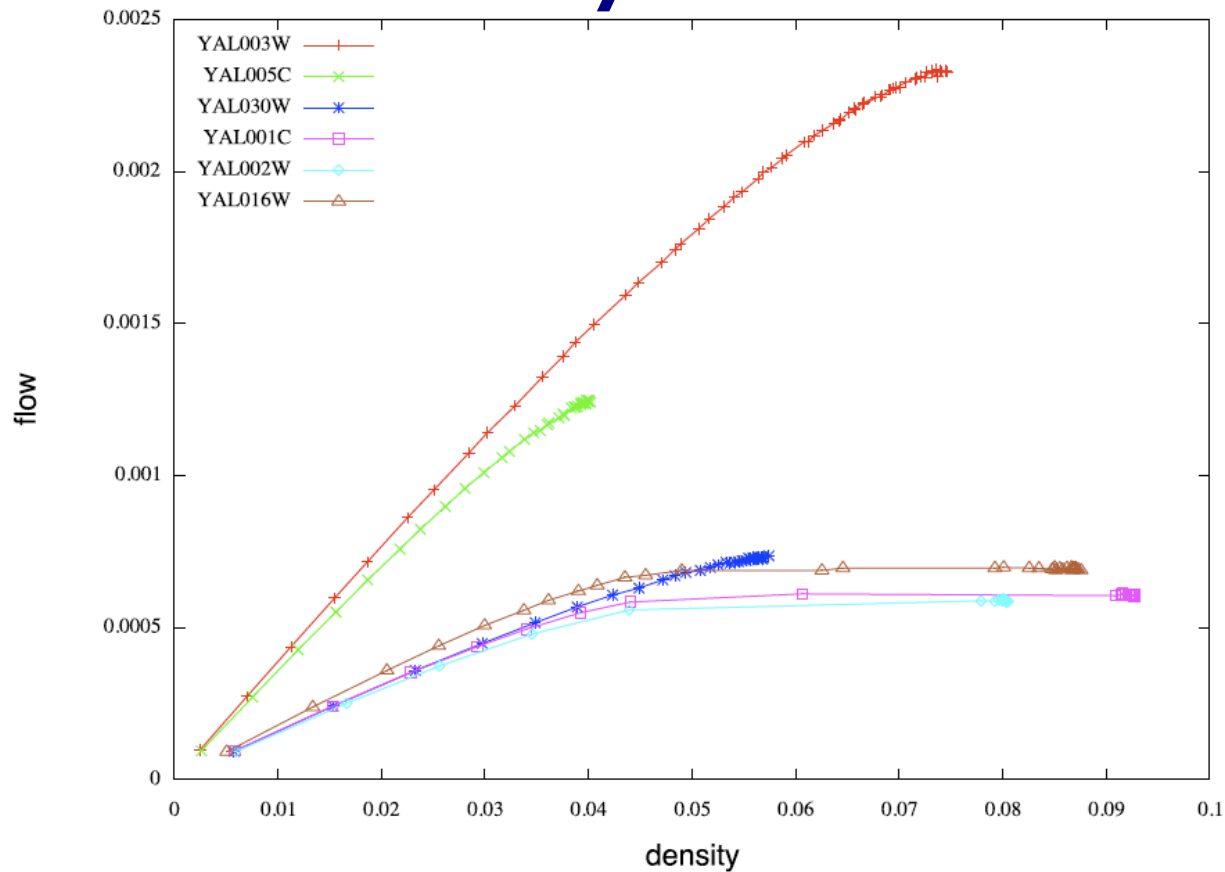


Analysis of 500 mRNA sequences from yeast





Analysis of 500 mRNA sequences from yeast



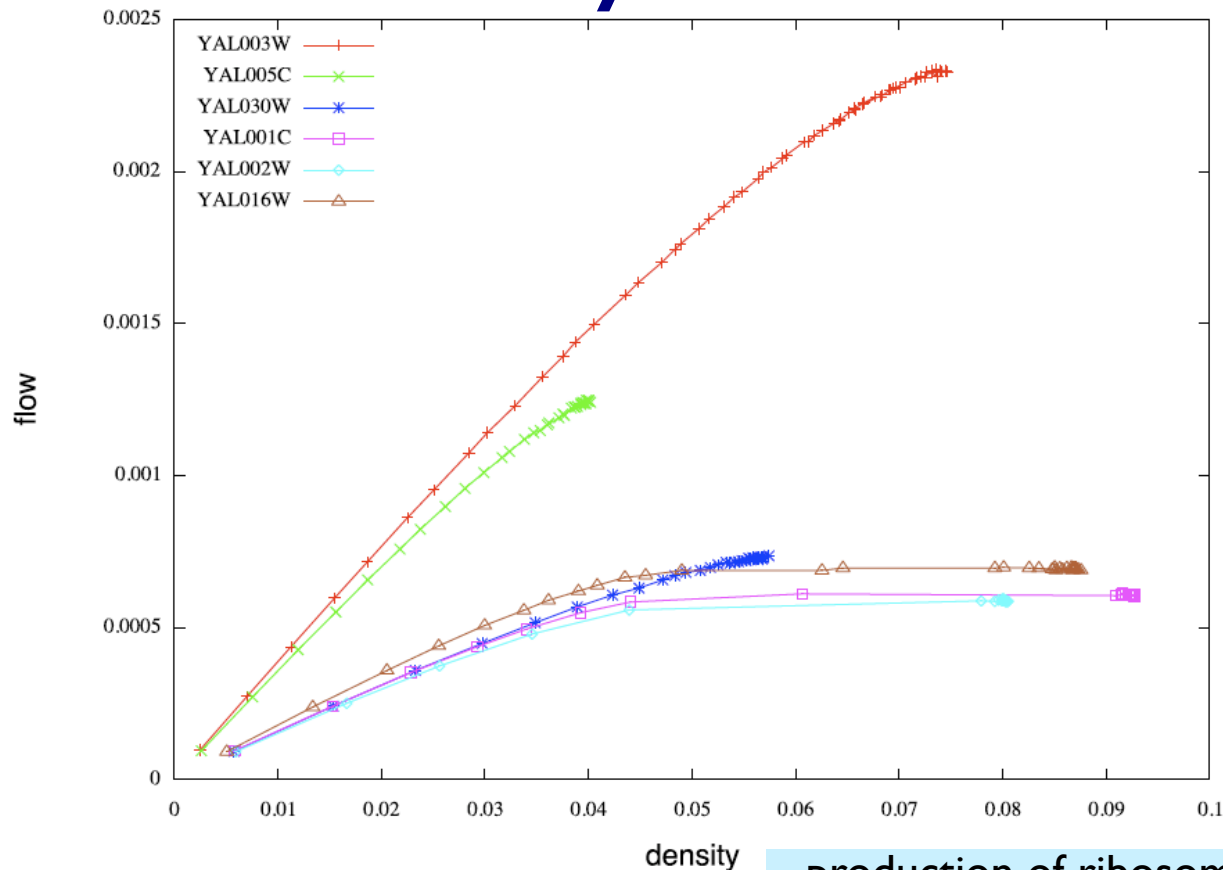
Two main types of transitions:

-Type-I: non-ribosomal proteins

-Type-II: ribosomal proteins



Analysis of 500 mRNA sequences from yeast



Two main types of transitions:

-Type-I: non-ribosomal proteins

-Type-II: ribosomal proteins



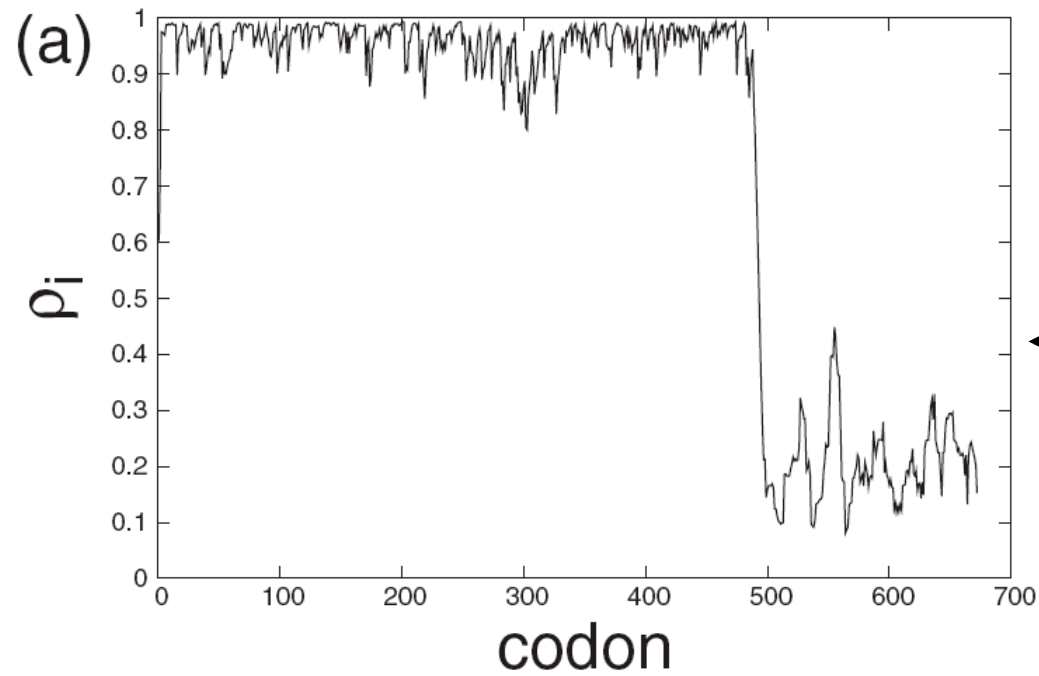
- production of ribosomes costs much energy to the cell; their production is tightly regulated (*Martin et al, Cell, 2004*).

-our results indicate that this production is also regulated at the translational level

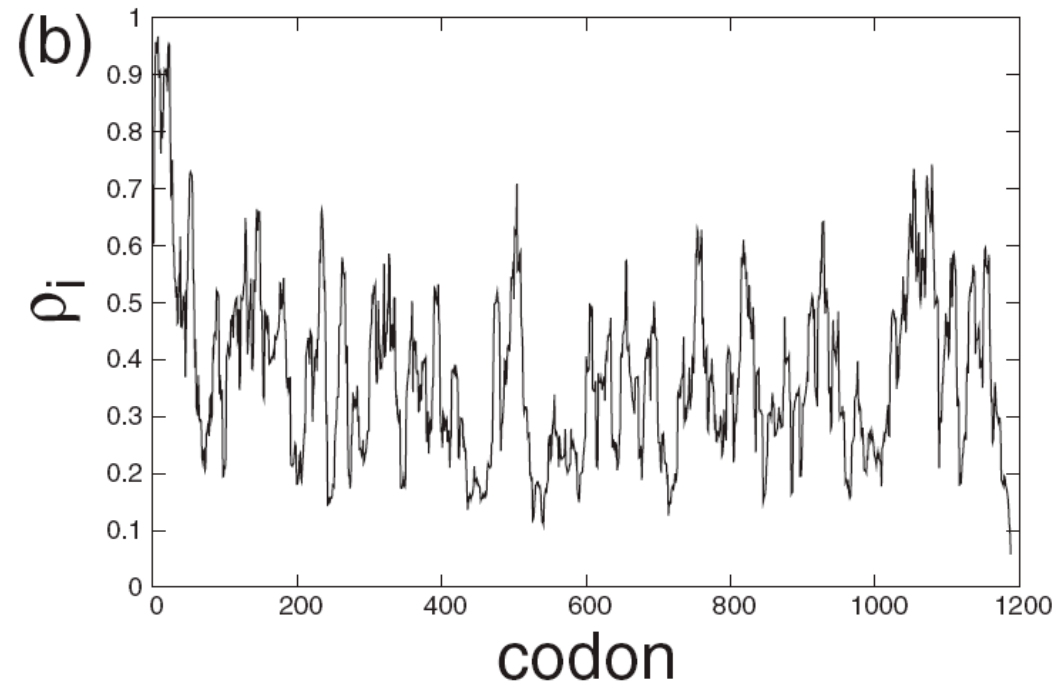
- other types of proteins are produced at a constant rate if α beyond α_{crit} .



Density profiles



← traffic jam;
abrupt transition



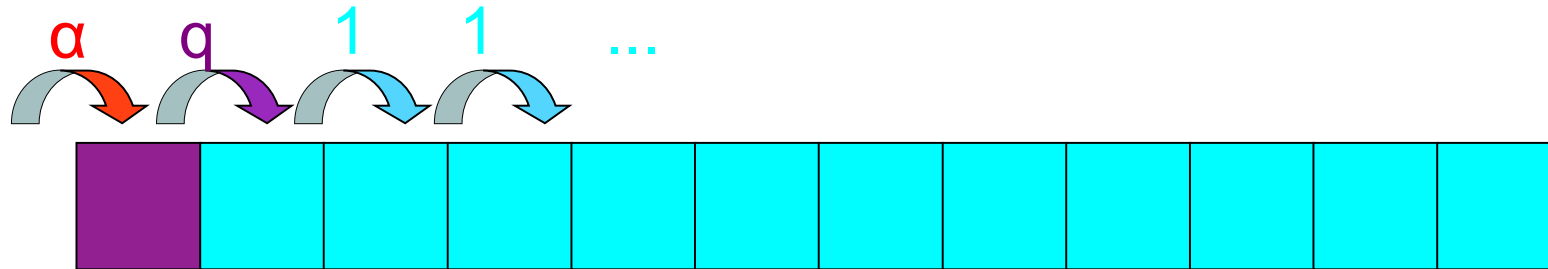
← no traffic jam;
smooth transition



One rare codon at the beginning:

$$p_1 = q$$

$$p_i = 1 \text{ for } i = 2, \dots, N$$



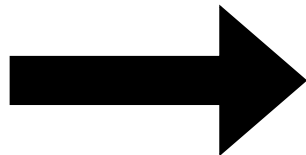
$$u_N = 1$$

$$u_{N-1} = 1$$

...

$$u_1 = q$$

$$u_0 = \alpha(1 - F/u_1 + F) = F \implies u_1 = \frac{\alpha F}{\alpha + \alpha F - F}$$



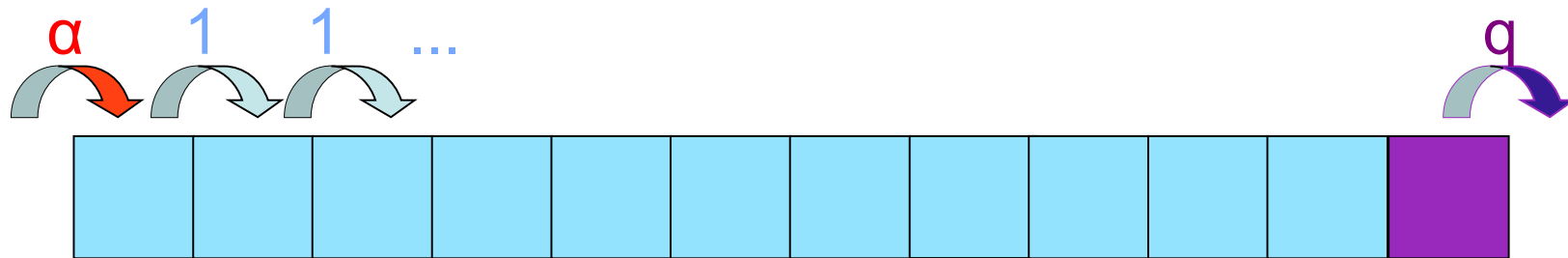
$$F = \frac{\alpha q}{\alpha + q - \alpha q}$$

$\frac{\partial F}{\partial \alpha}$ continuous in the range $0 < \alpha < 1 \implies$ smooth dependence of F on α



One rare codon at the end:

$$p_i = 1 \text{ for } i = 1, \dots, N - 1$$
$$p_N = q$$



$$u_N = q$$
$$u_{N-1} = 1 - \rho_N + F = 1 - F/u_N + F$$
$$\dots$$
$$u_1 = 1 + F/u_2 + F$$
$$u_0 = \alpha(1 - F/u_1 + F) = F \implies u_1 = \frac{\alpha F}{\alpha + \alpha F - F}$$



Closed form for u_{N-i} as a function of $u_N = q$ and F :

$$u_{N-i} = \frac{(q-1)F^{i+1} + F - q}{(q-1)F^i + F - q}$$

Equating this formula to the expression obtained from the right boundary condition:

$$\frac{\alpha F}{\alpha + \alpha F - F} = \frac{(q-1)F^N + F - q}{(q-1)F^{N-1} + F - q}$$

\Rightarrow polynomial of N -th order. Neglecting F^N ($0 < F < 1$ and N large):

$$F = \begin{cases} \alpha & \text{if } \alpha < q \\ q & \text{if } \alpha > q \end{cases}$$

$\frac{\partial F}{\partial \alpha}$ discontinuous at $\alpha = q \Rightarrow$ phase transition of first order



M rare codons with hopping probabilities q_1, q_2, \dots, q_M , well separated:
position of the slowest codon; first codon slow or not

A

- slowest codon is at site $i=1$
→ no queueing transition

B

- there is a slow codon at site $i=1$, but it is not the slowest one.

$$\alpha_c = \frac{q_{\min} q_1}{q_1 + q_1 q_{\min} - q_{\min}}$$

C

- slowest codon: q_{\min} at site $i>1$
- there is no slow codon at site $i=1$

$$\alpha_c = q_{\min}$$



Traffic dynamics on mRNA sequences is related to the biological function of proteins

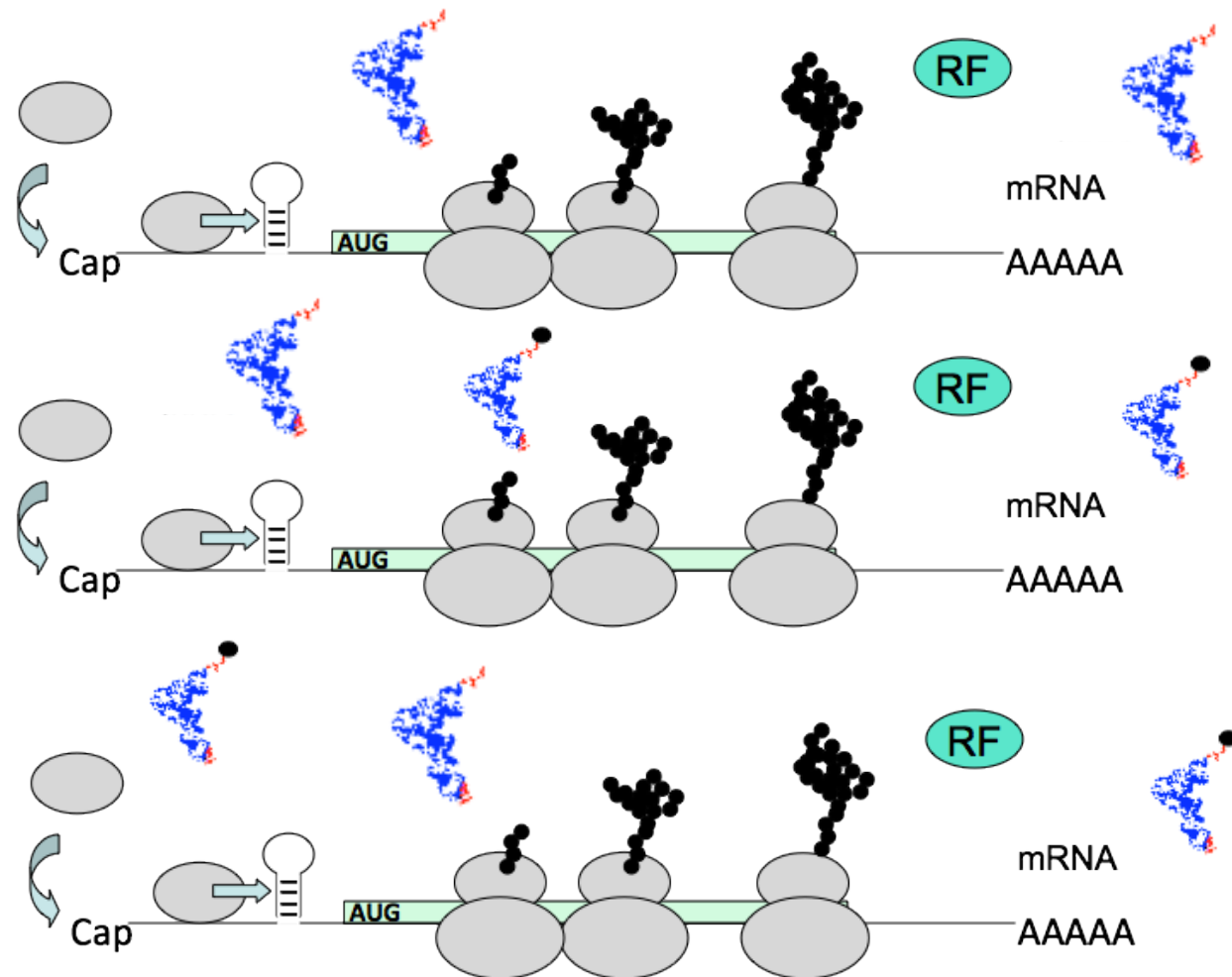
Further work on translation:

Biochemical cycle of ribosomes

Luca Ciandrini

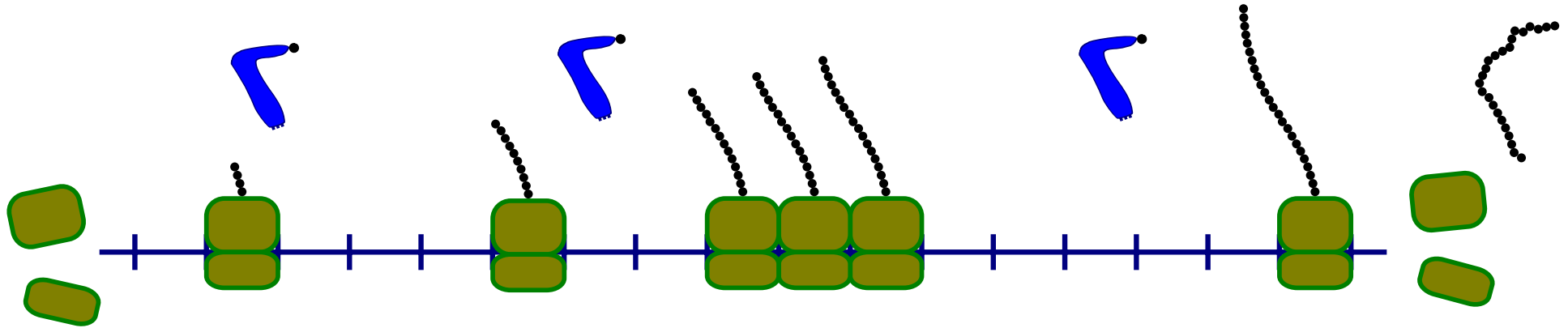
Competition for resources

Chris Brackley



mRNA Translation

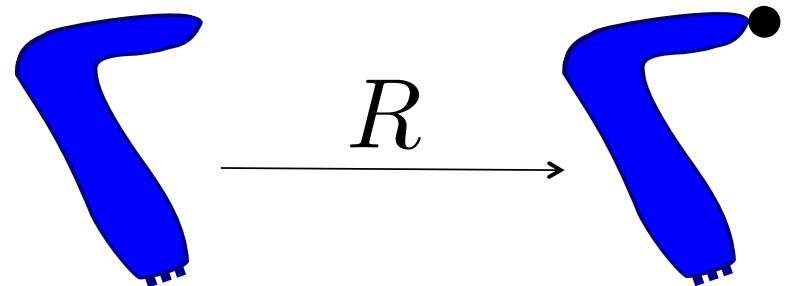
Ribosomes wait until they encounter the correct aa-tRNA



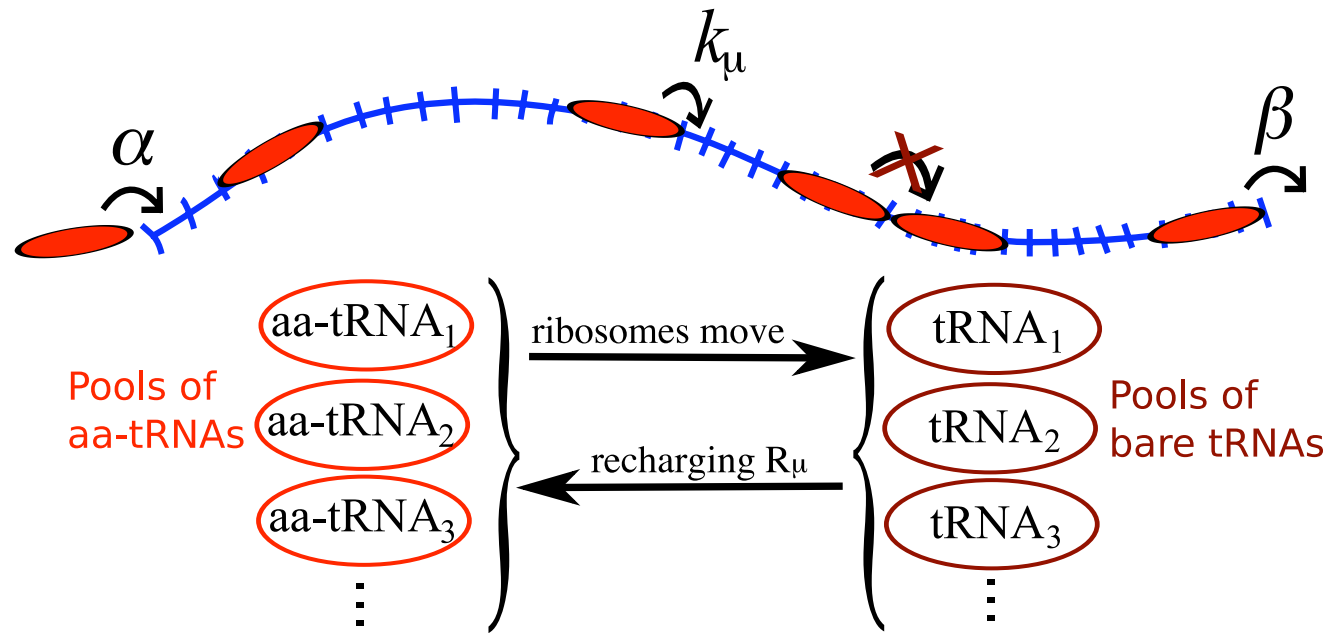
Ribosomes attempt to bind at a certain rate

It takes a finite time for the ribosome to dissociate

- tRNAs are not used up
- Bare tRNA are left
- These are recharged with new amino acids at a finite rate R



Translation



- Allow hopping rates to vary with the number of available aa-tRNAs
- Total number of tRNAs is fixed
- Rate of recharging tRNAs \rightarrow aa-tRNAs is finite

C.A. Brackley, M. C. Romano, C. Grebogi and M. Thiel "Limited resources in a driven diffusion process" Phys. Rev. Lett. **105** 078102 (2010)

C.A. Brackley, M. C. Romano and M. Thiel "Slow Sites in an Exclusion Process with Limited Resources" Phys. Rev. E **82** 051920 (2010)

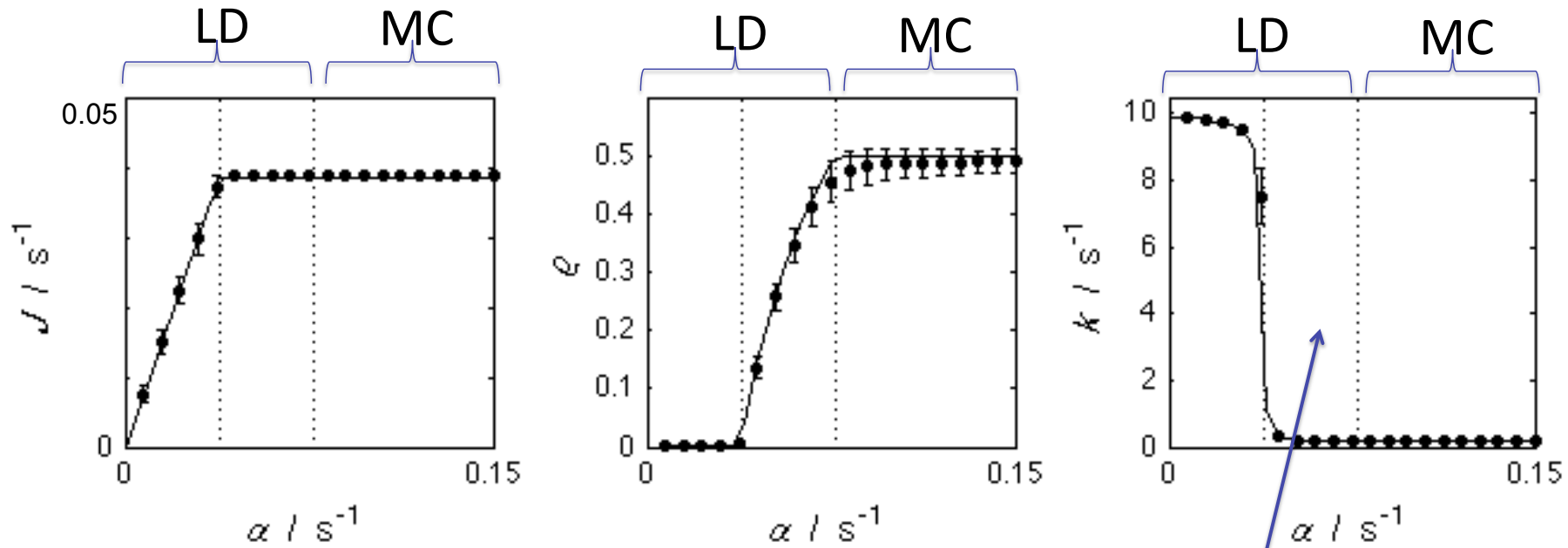
Balance of Supply and Demand

- As **demand** increases, **supply** can no longer keep up.
- It leads to depletion of aa-tRNAs and **queuing**.

Unexpected effects arise due to interaction between different mRNAs via the pool of resources.

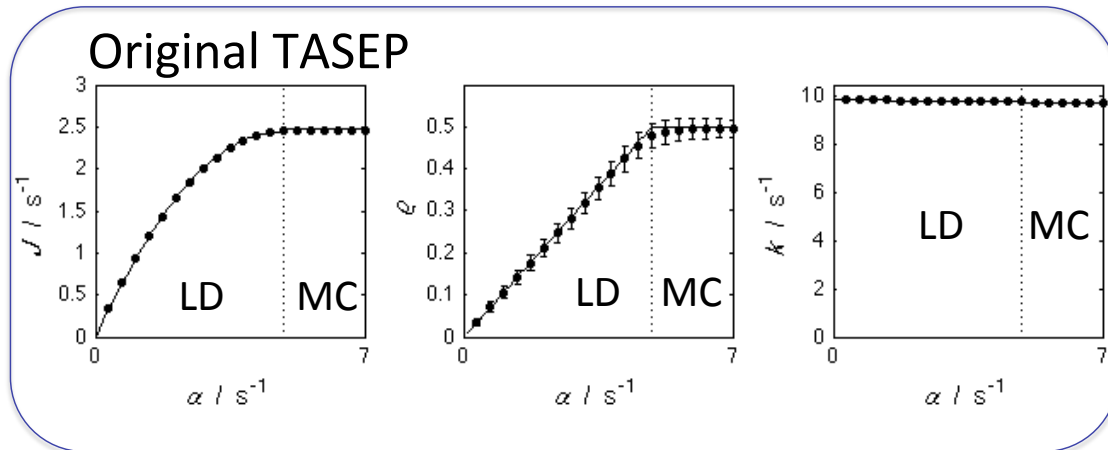
- Resources used on one mRNA can lead to **bottlenecks** on another.
- Bottlenecks on one mRNA can **free resources** for use on another.

TASEP with Recharging (Realistic Parameters)



A new regime within the LD phase

Limited Resources Regime



The rate at which aa-tRNAs are replenished limits the rate at which they can be used.

When might this be important in the real cell?

Changes in supply and demand could result from:

- up-regulation of ribosome biogenesis.
- change in nutrient availability – **amino acid starvation**.
- change in availability of recharging enzymes.
- change in mRNA abundance during different phases of the cell cycle.

Important consequences for **synthetic biology**:
changing the genome changes the demand on resources.
also need to consider the supply.

C.A. Brackley, M. C. Romano, C. Grebogi, and M. Thiel, "*Limited resources in a driven diffusion process*," *Phys. Rev. Lett.* **105** 078102 (2010)

C. A. Brackley, M. C. Romano and M. Thiel "*The Dynamics of Supply and Demand in mRNA Translation*" *PLoS Comp. Biol.* **7** e1002203 (2011)

Can codon order give control of protein production?

Rate of elongation depends on **abundance** of required aa-tRNA

In the model organism *Saccharomyces cerevisiae* (bakers yeast):
41 tRNA species, but 20 amino acids – redundancy in the code?

- Some tRNAs are rare – slow elongation of these codons
- Some tRNAs are common – fast elongation of these codons

Some amino acids have both a slow codon and a fast codon associated with them:

Why use the slow codon?

How does the pattern of codon usage effect:

- Protein production rate.
- Ribosome density on the mRNA.

Theoreticians

- Chris Brackley
- Luca Ciandrini
- Celso Grebogi
- Mamen Romano
- Marco Thiel

Romano, Thiel, Stansfield and Grebogi, PRL **102**, 198104 (2009)

Brackley, Romano, Grebogi and Thiel, PRL **105**, 078102 (2010)

Ciandrini, Stansfield and Romano, PRE **81**, 051904 (2010)

Brackley, Romano, and Thiel, Phys. Rev. E **82**, 051920 (2010)

Brackley, Romano, Thiel, PLoS Comput. Biol. **7**, e1002203 (2011)

Experimentalists

- Russell Betney
- Alain Kemp
- Ian Stansfield

