Role of the particle's stepping cycle in a TASEP:
a model of mRNA translation

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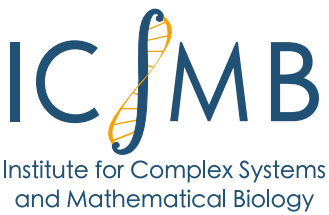
Edinburgh, 9th December 2011



Outline

1. Introduction: mRNA translation for dummies
2. Particle's stepping cycle: two-state model
3. Non-localised traffic jams
4. Back to Biology: what can I do with that?
5. Conclusions and further developments

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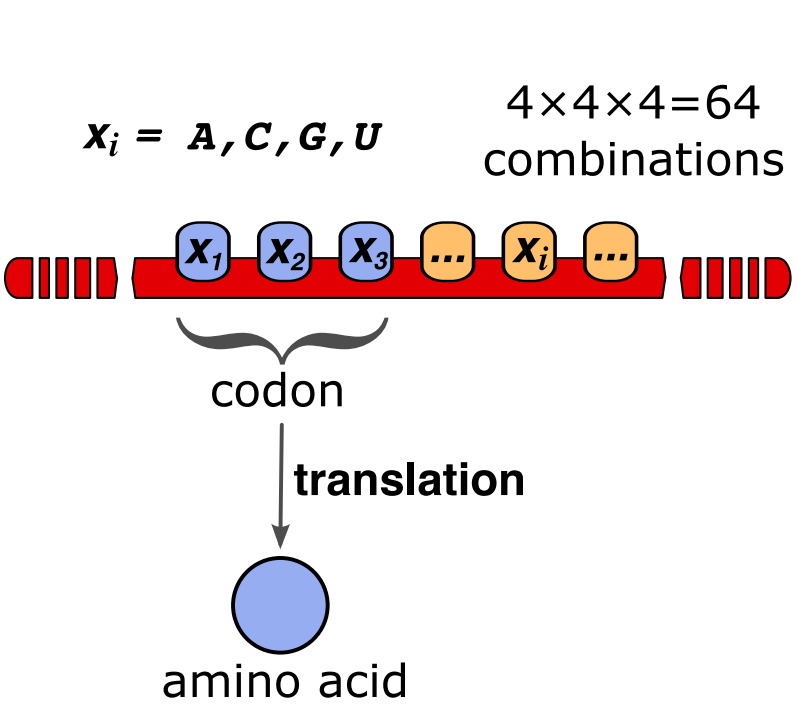
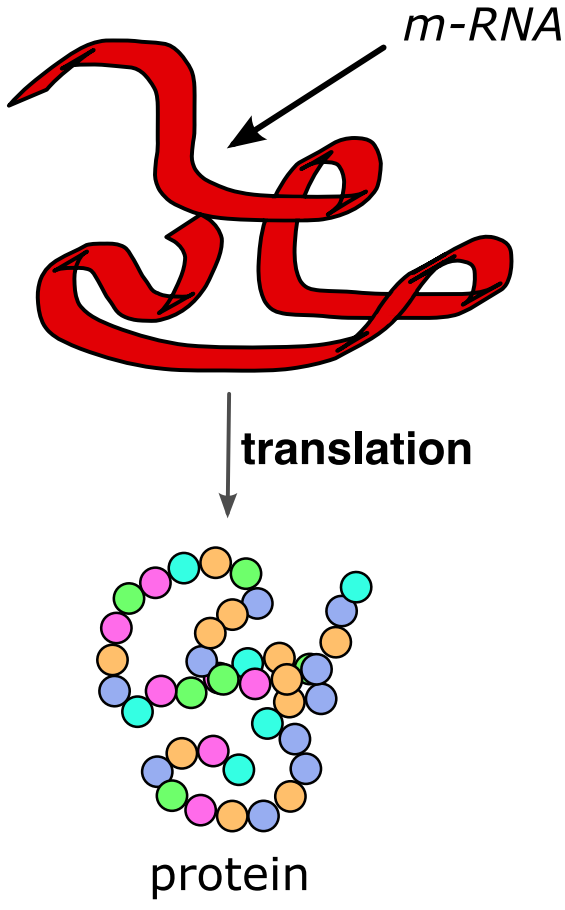
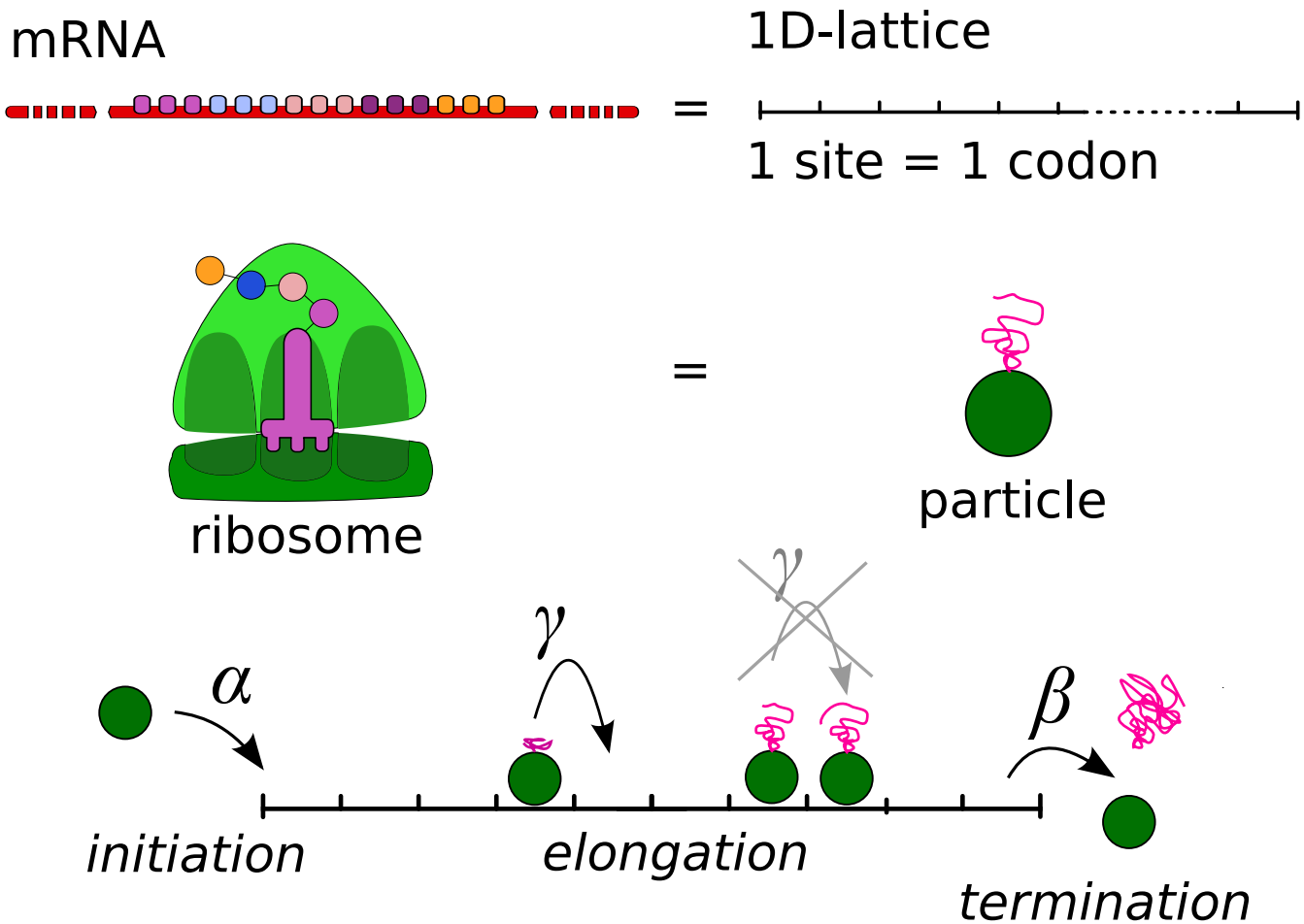
The central dogma of molecular biology

DNA $\xrightarrow{\text{transcription}}$ mRNA $\xrightarrow{\text{mRNA translation}}$ proteins



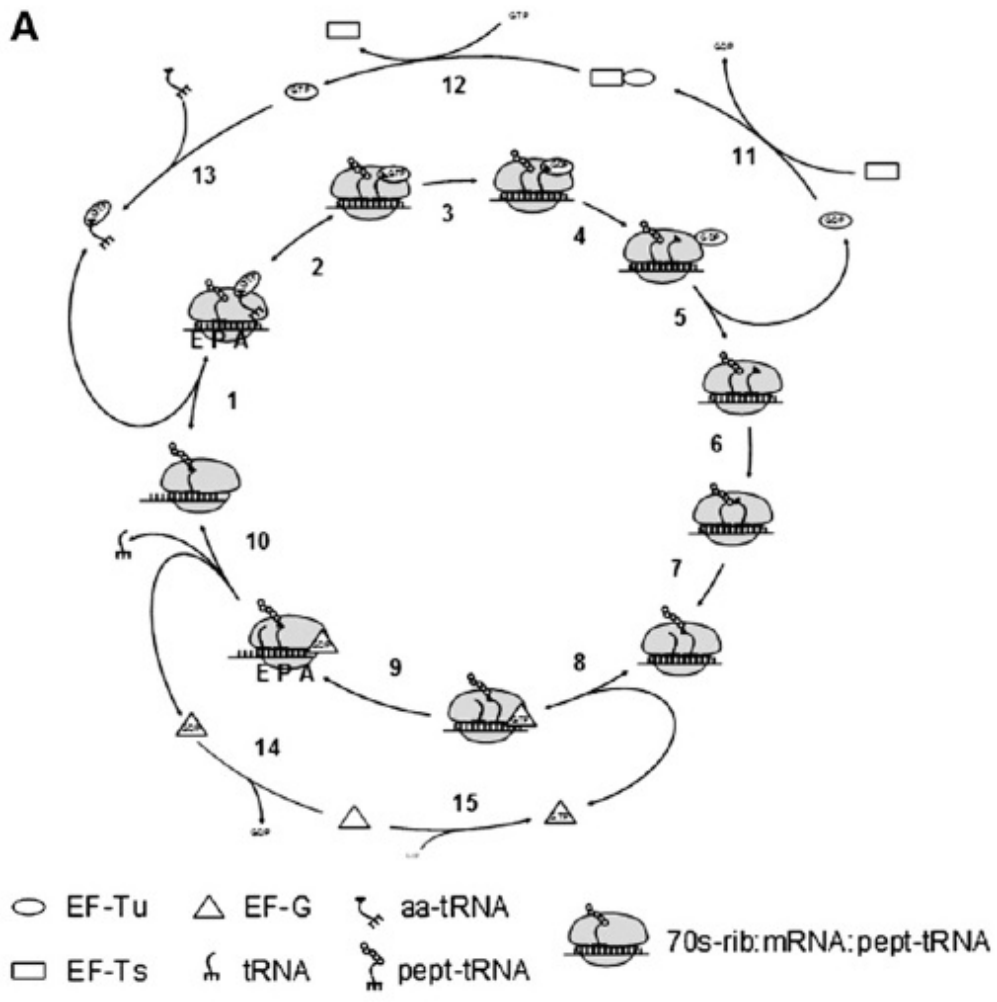


TASEP has been introduced to mimic mRNA translation



C. T. MacDonald, J. H. Gibbs, A. C. Pipkin. *Biopolymers*, 6(1):1–5, 1968

The ribosome's stepping cycle can be rather complicated...



Zouridis H, Hatzimanikatis V, Biophys J. 2007;92(3).
A model for protein translation: polysome self-organization leads to maximum protein synthesis rates.

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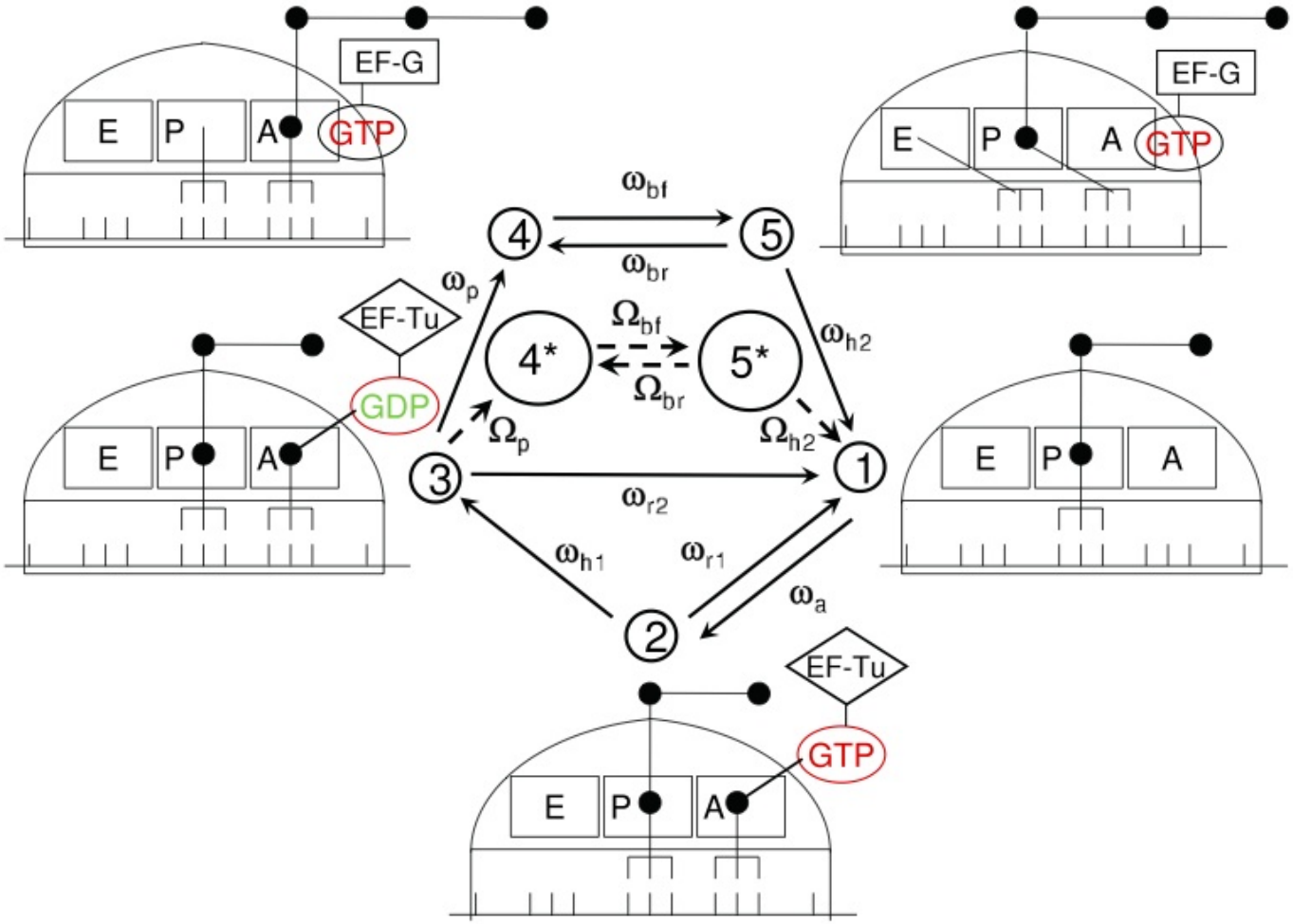

Sharma AK, Chowdhury D, Phys. Biol. 2011;8(2).

Distribution of dwell times of a ribosome: effects of infidelity, kinetic proofreading and ribosome crowding.

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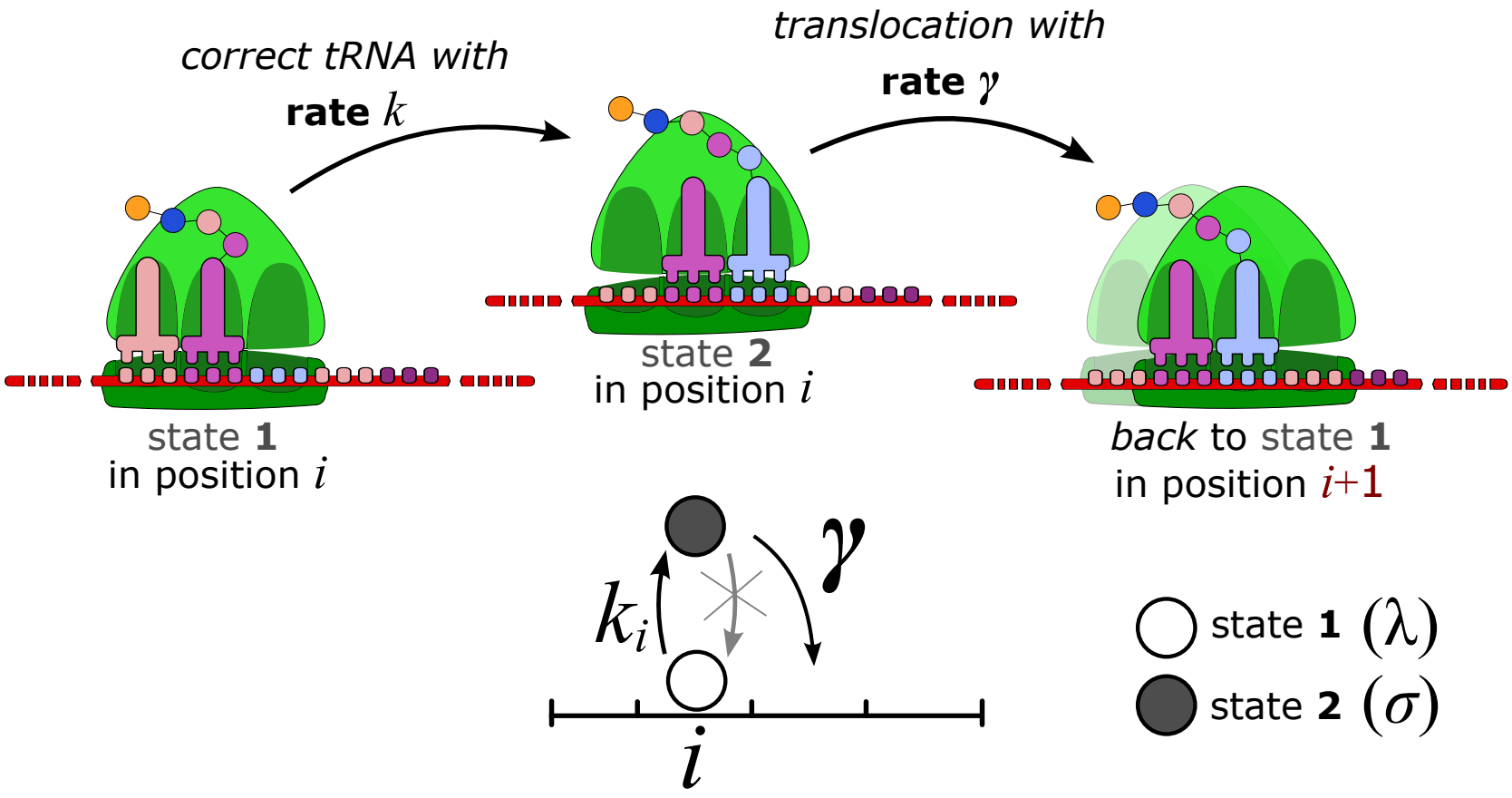
Two-state model



S. Klumpp, Y. Chai, and R. Lipowsky, *Phys. Rev. E*, 78:041909, 2008

L. Ciandrini, I. Stansfield, and M. C. Romano, *Phys. Rev. E*, 81:051904, 2010

Occupation numbers and densities

The occupation number of site i is $n_i = 0, 1, 2$ ($\sqcup$, $\bigcirc$, $\bullet$).

The dynamical rules can be written as

$$\begin{aligned} 1 &\to 2 && \text{with rate } k_i \\ 20 &\to 01 && \text{with rate } \gamma. \end{aligned}$$

And we introduce the densities:

$$l_i = n_i(2 - n_i) \qquad s_i = \frac{n_i(n_i - 1)}{2}$$

$$\lambda_i = \langle l_i \rangle \qquad \sigma_i = \langle s_i \rangle$$

$$\rho_i = \lambda_i + \sigma_i \ .$$

Mean-field (MF) equations

The flow equations (MF) for the densities are:

$$\begin{cases} \dfrac{d\lambda_i}{dt} = \sigma_{i-1}(1-\lambda_i-\sigma_i)\gamma - k\lambda_i \\ \\ \dfrac{d\sigma_i}{dt} = k\lambda_i - \sigma_i(1-\lambda_{i+1}-\sigma_{i+1})\gamma \end{cases}$$

+ steady state $(\dfrac{d\lambda_i}{dt} = \dfrac{d\sigma_i}{dt} = 0)$.

The incoming and outgoing currents at site i are:

$$J_+^i = \sigma_{i-1}(1-\lambda_i-\sigma_i)\gamma, \qquad J_-^i = \sigma_i(1-\lambda_{i+1}-\sigma_{i+1})\gamma \ .$$

Our mean-field assumes $\langle s_i s_j \rangle \simeq \langle s_i \rangle \langle s_j \rangle$ and $\langle l_i s_j \rangle \simeq \langle l_i \rangle \langle s_j \rangle$, which is different than simply $\langle n_i n_j \rangle \simeq \langle n_i \rangle \langle n_j \rangle$

Periodic Boundary Conditions (PBC)

$$\begin{cases} \dfrac{d\lambda}{dt} = \sigma(1-\lambda-\sigma)\gamma - k\lambda \\ \\ \dfrac{d\sigma}{dt} = k\lambda - \sigma(1-\lambda-\sigma)\gamma \end{cases}$$

$$\downarrow$$

$$J = \sigma(1-\lambda-\sigma)\gamma$$

$$\lambda = \frac{J}{k}$$

$$\sigma = \rho - \lambda = \rho - \frac{J}{k}$$

L. Ciandrini, I. Stansfield, and M. C. Romano, *Phys. Rev. E*, 81:051904, 2010

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$$\downarrow$$

$$J = \sigma(1-\lambda-\sigma)\gamma$$

$$\lambda = \frac{J}{k}$$

$$\sigma = \rho - \lambda = \rho - \frac{J}{k}$$

$$w := k/\gamma$$

$$J = k\frac{\rho(1-\rho)}{w+(1-\rho)}$$

$$\lambda = \frac{\rho(1-\rho)}{w+(1-\rho)}$$

$$\sigma = w\left[\frac{\rho}{w+(1-\rho)}\right]$$

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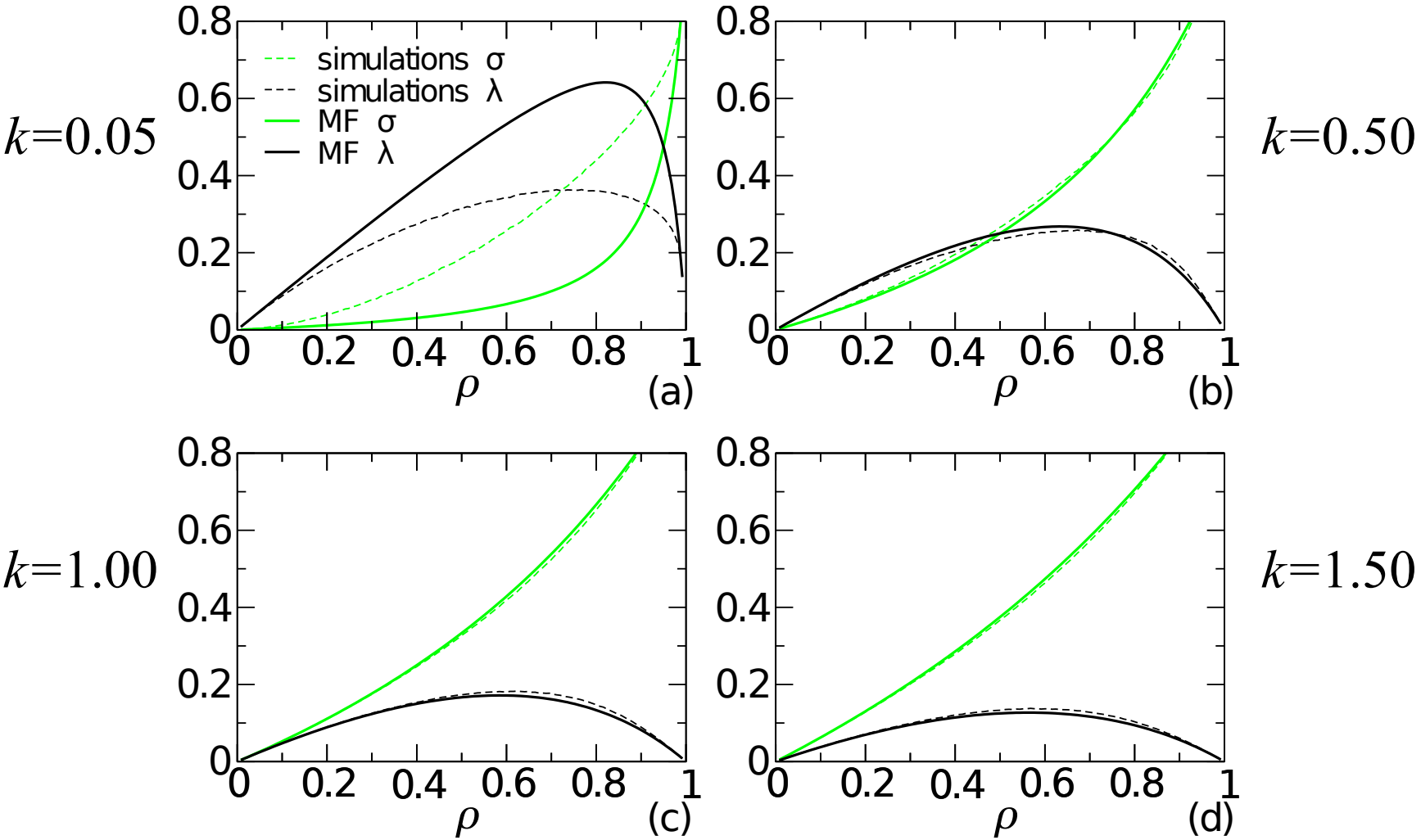
Comparison between simulations (- -) and MF (–)

For small k the MF underestimates transitions toward the state 2



The current is simply $J = k\lambda$.

Periodic Boundary Conditions (PBC) - MC densities

Where the value of ρ for which the current is maximal is

$$\rho^* = 1 - \chi \,,$$

and the maximal value of the densities are

$$\lambda^* = 1 - 2\chi \,, \qquad \sigma^* = \chi \,.$$

$$w := k/\gamma$$

$$\chi := w(\sqrt{1 + 1/w} - 1)$$

Open Boundary Conditions (OBC)

$$\begin{cases} \dfrac{d\lambda_i}{dt} = \sigma_{i-1}(1-\lambda_i-\sigma_i)\gamma - k\lambda_i \\ \\ \dfrac{d\sigma_i}{dt} = k\lambda_i - \sigma_i(1-\lambda_{i+1}-\sigma_{i+1})\gamma \end{cases}$$

+ boundary conditions:

$$\frac{d\lambda_1}{dt} = \alpha(1-\lambda_1-\sigma_1) - k\lambda_1$$

$$\frac{d\sigma_L}{dt} = k\lambda_L - \beta\sigma_L$$

Open Boundary Conditions (OBC)

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+ boundary conditions:

$$\begin{aligned} \frac{d\lambda_1}{dt} &= \alpha(1-\lambda_1-\sigma_1) - k\lambda_1 \\ \frac{d\sigma_L}{dt} &= k\lambda_L - \beta\sigma_L \end{aligned}$$

$\rightarrow$ we can write a recursive map for the density σ_i:

$$\sigma_{i+1} = 1 - J\left(\frac{1}{k} + \frac{1}{\gamma\sigma_i}\right)$$

Maximal Current Principle in OBC

The boundaries are substituted by reservoirs of particles and the dynamics between the reservoir and the lattice is assumed to be the same as in the bulk. J. Krug, *Phys. Rev. Lett.*, 67:1882, 1991

The *Maximal Current Principle* states that J in the MC regime is given by

$$J_{\mathrm{MC}} = \max_{\rho \in [\rho_{L+1}, \rho_0]} J_{\mathrm{PBC}}(\rho),$$

where ρ_0 and ρ_{L+1} are respectively the densities of the reservoirs of particles at the left and the right boundaries and are chosen to realize the injection and depletion parameters α and β.

$$\rho_0 = \lambda_0 + \sigma_0 \ ,$$

$$\alpha = \sigma_0 \gamma \ , \qquad \beta = \gamma(1 - \rho_{L+1})$$

The Maximal Current Principle locates the critical points

The critical points are obtained by equating σ_0 with $\sigma*$ and ρ_{L+1} with ρ^* . $[w := k/\gamma,\ \chi := w(\sqrt{1+1/w}-1)]$

Low Density (LD) phase $[\alpha < \beta\ ,\ \alpha < \gamma\,\chi]$

$$\rho = \frac{\alpha(k+\gamma)}{\gamma(k+\alpha)}\ , \qquad J = \alpha\frac{k(\gamma-\alpha)}{\gamma(k+\alpha)}$$

High Density (HD) phase $[\beta < \alpha\ ,\ \beta < \gamma\,\chi]$

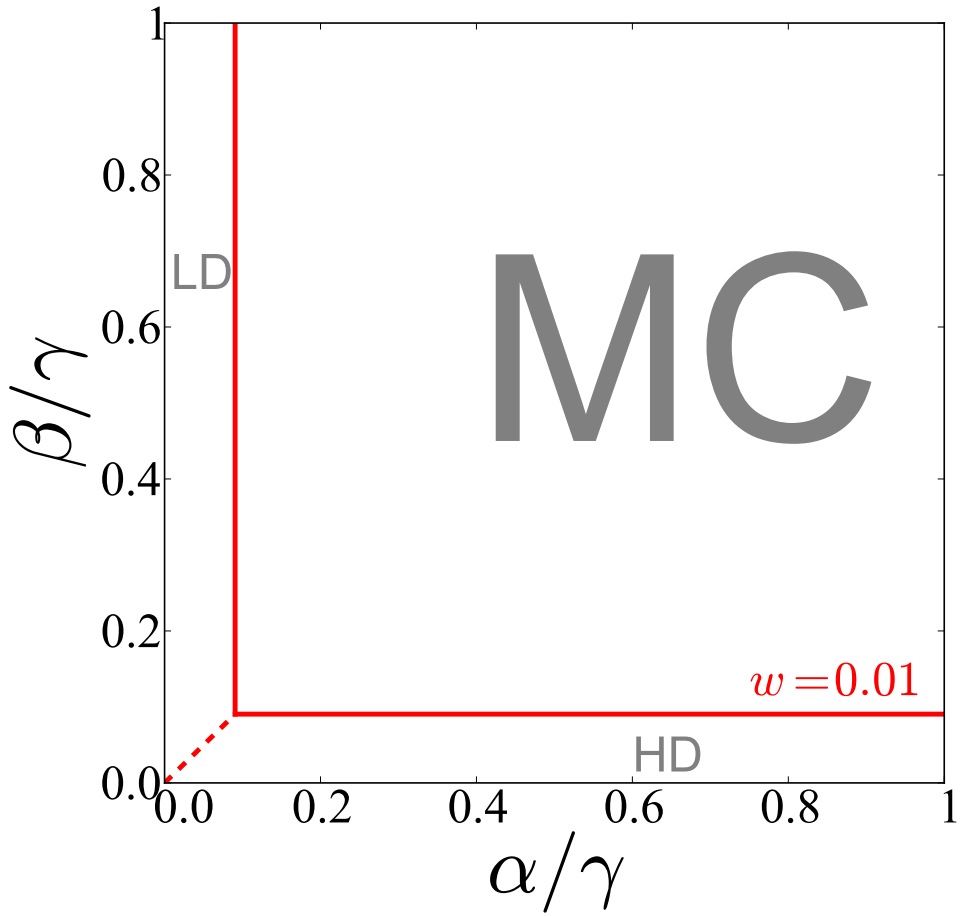
$$\rho = 1 - \frac{\beta}{\gamma}\ , \qquad J = \beta\frac{k(\gamma-\beta)}{\gamma(k+\beta)}$$

Maximal Current (MC) phase $[\alpha, \beta \geqslant \gamma\,\chi]$

$$\rho = 1-\chi\ , \qquad J = k(1-2\chi)$$

$[\sigma^* = \chi,\ \rho^* = 1-\chi]$

The critical points α_c and β_c depend on $w = k/\gamma$, but in the limit $w \to \infty$ (particles with only one state) we find the well known TASEP results.



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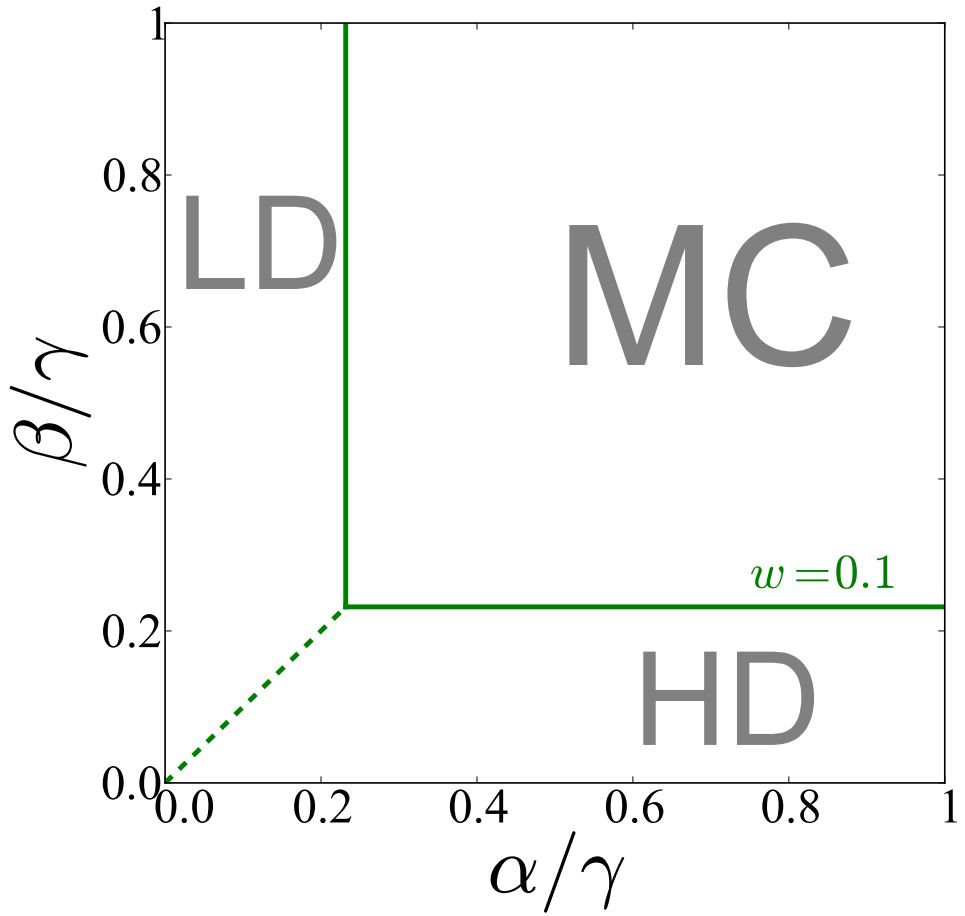

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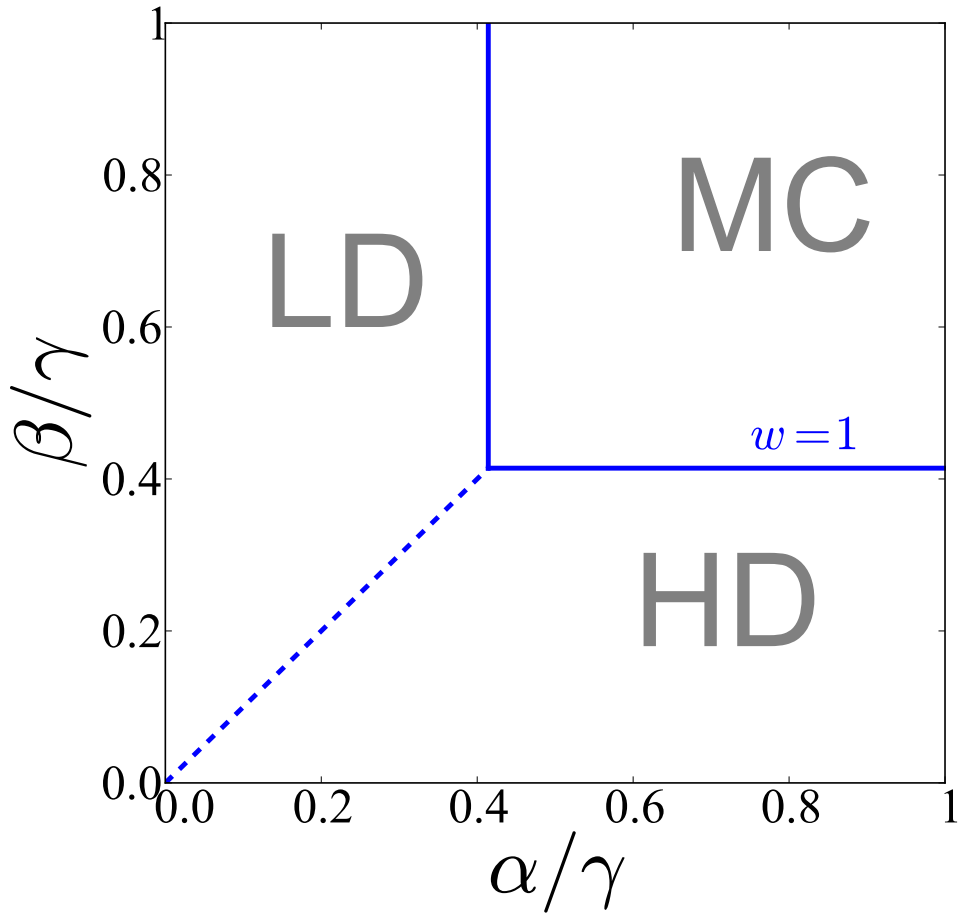

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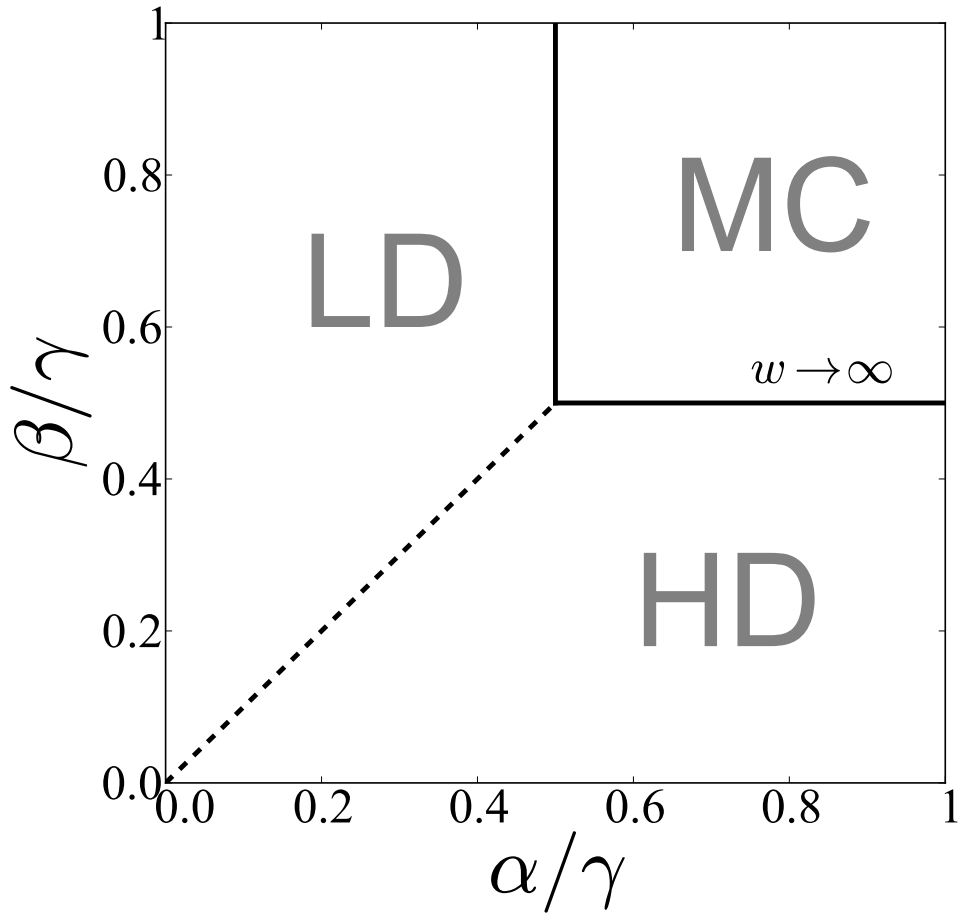

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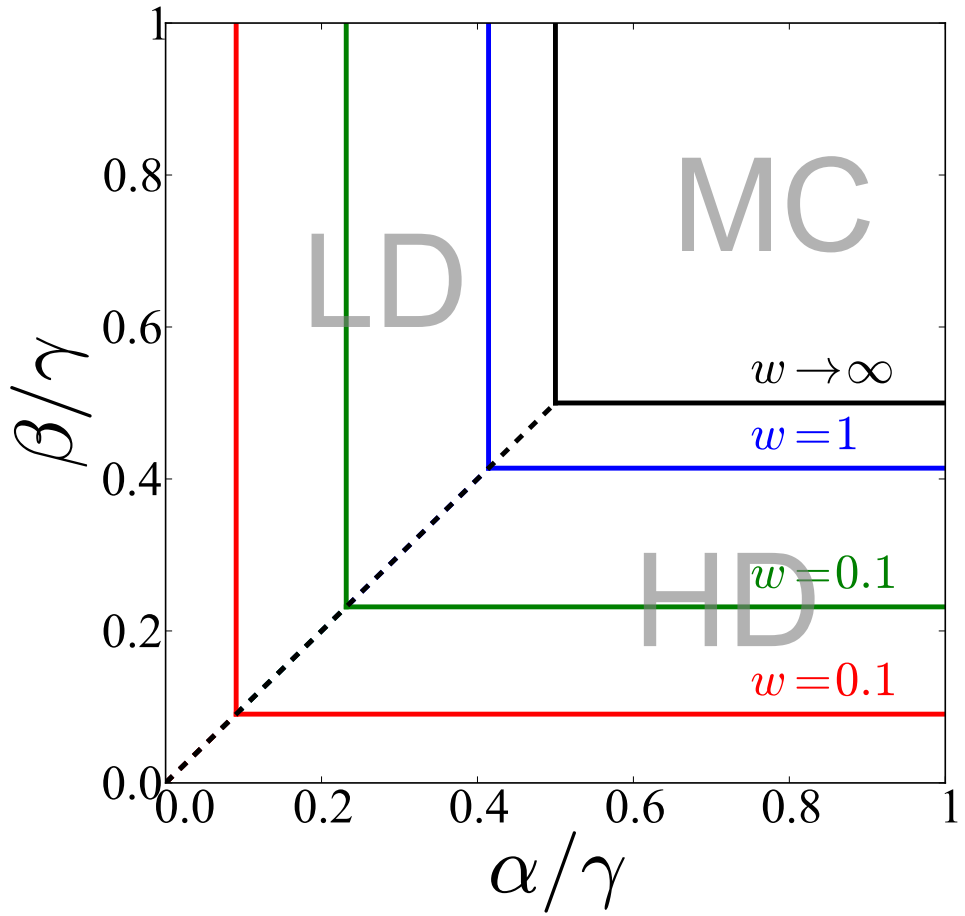

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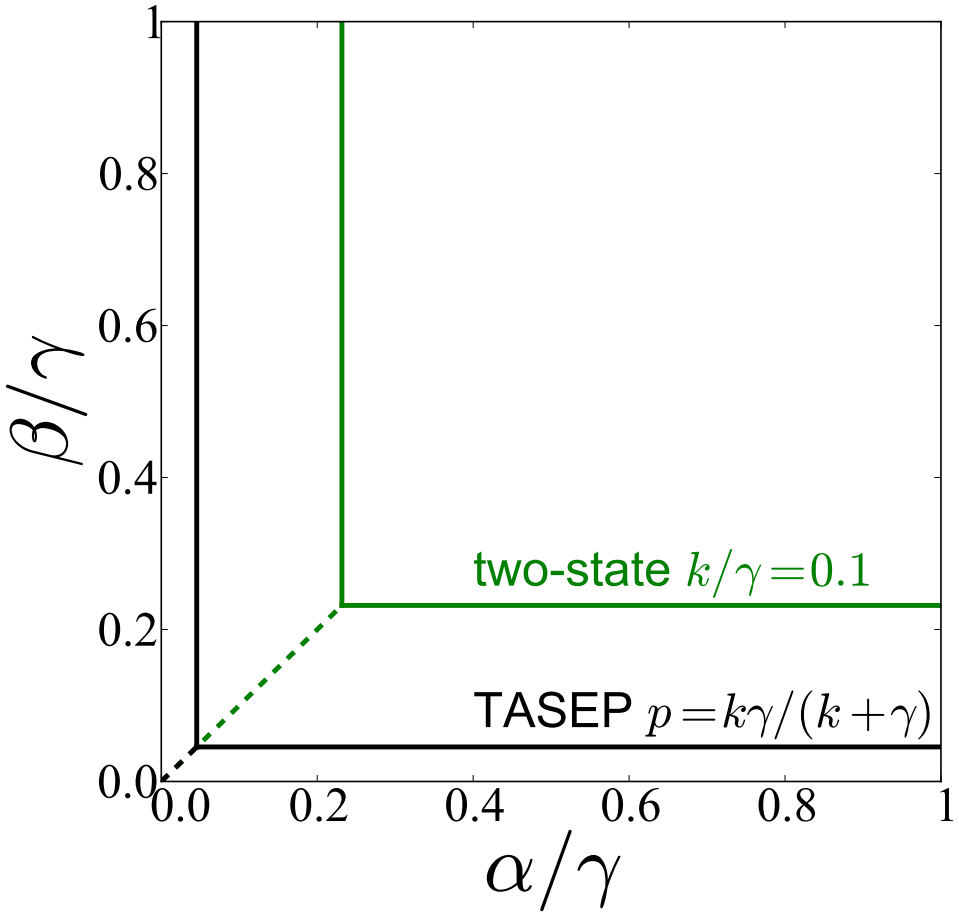
Two-state model is intrinsically different from the TASEP



TASEP with hopping rate
$p = k\gamma/(k+\gamma), \quad k/\gamma = 0.1$

The two-state model cannot be mapped onto a TASEP with effective hopping rates.
Critical points and steady-state quantities depend on the internal dynamics, but there are dynamical effects too...

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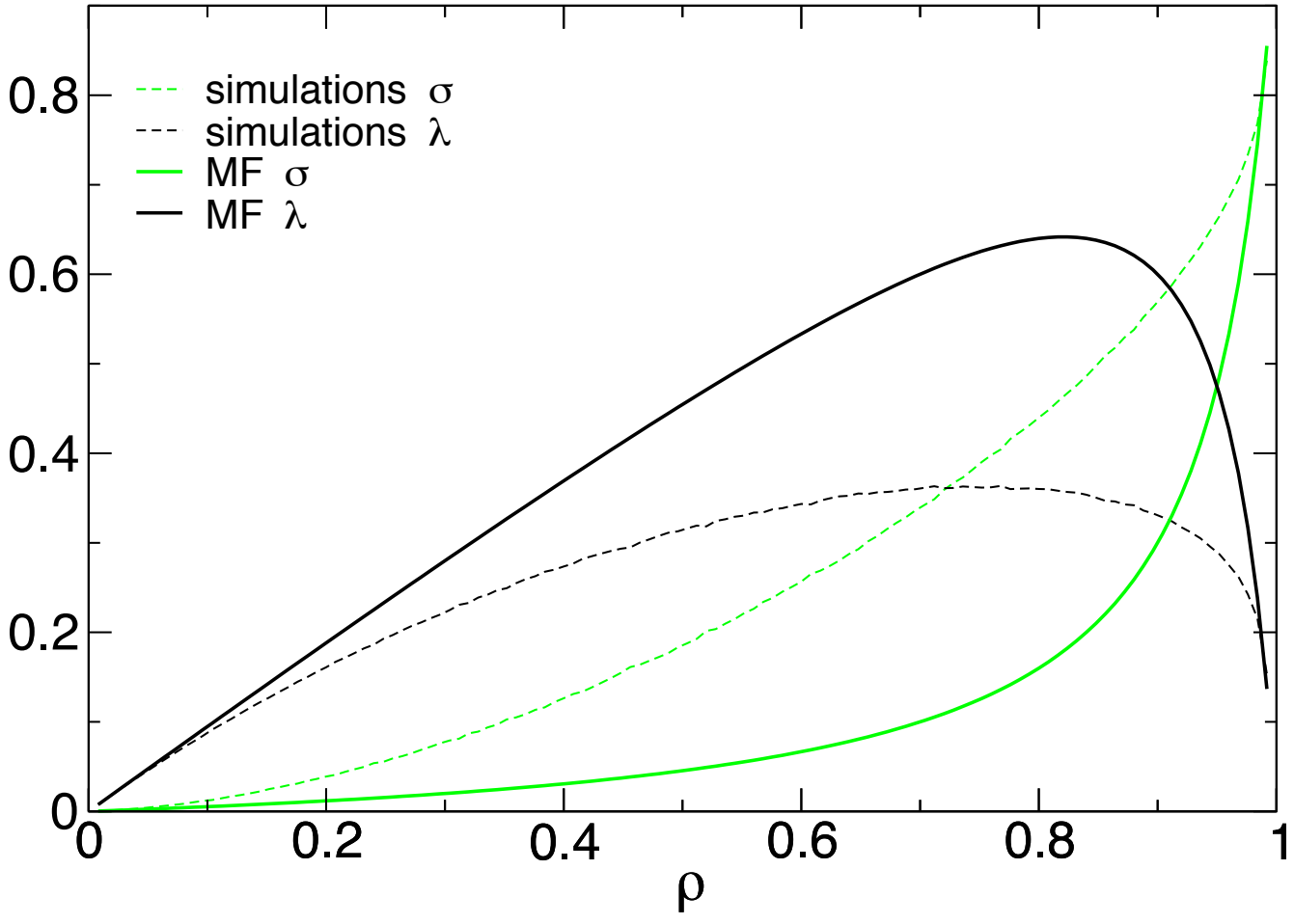
Non-localised traffic jams

Starting point: deviation MF-theory for small k/γ



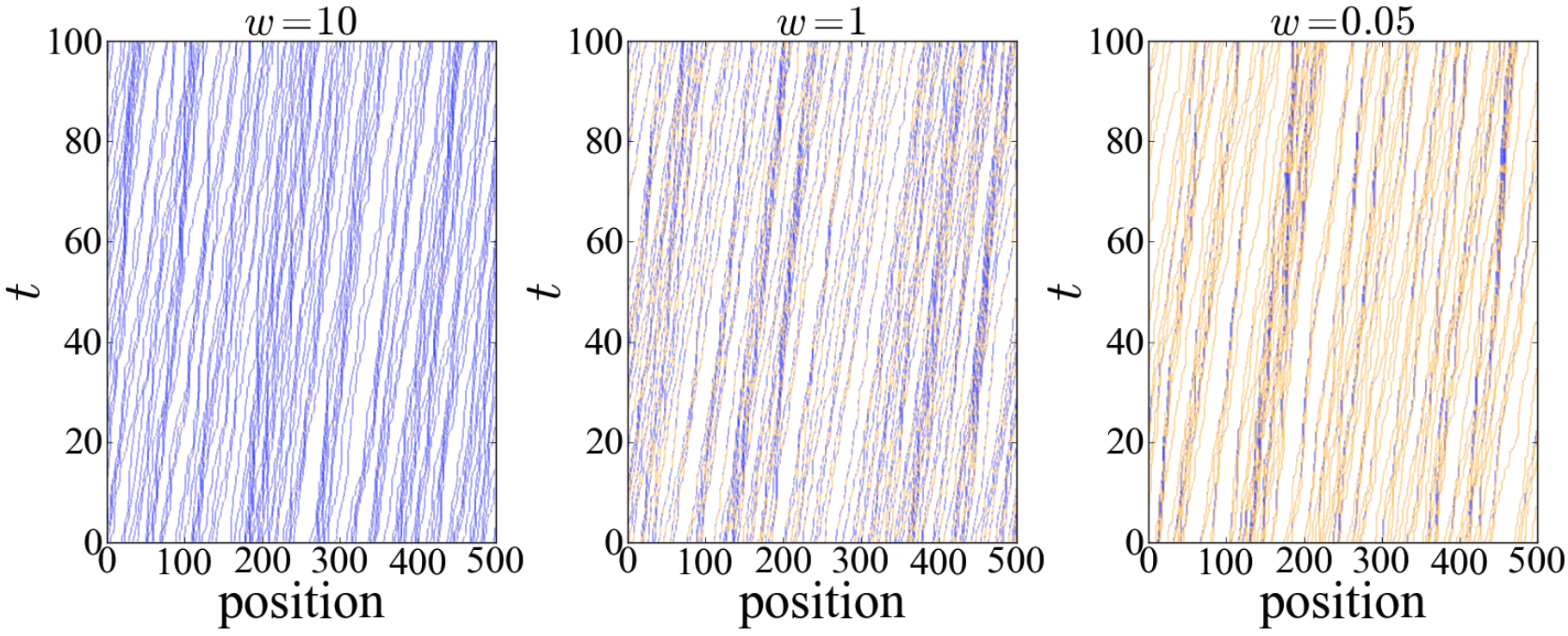
Work in progress...

(manuscript in preparation)

with M C Romano and A Parmeggiani (Université de Montpellier II)

Kymographs of the two-state model

The kymographs show non-localised traffic jams...



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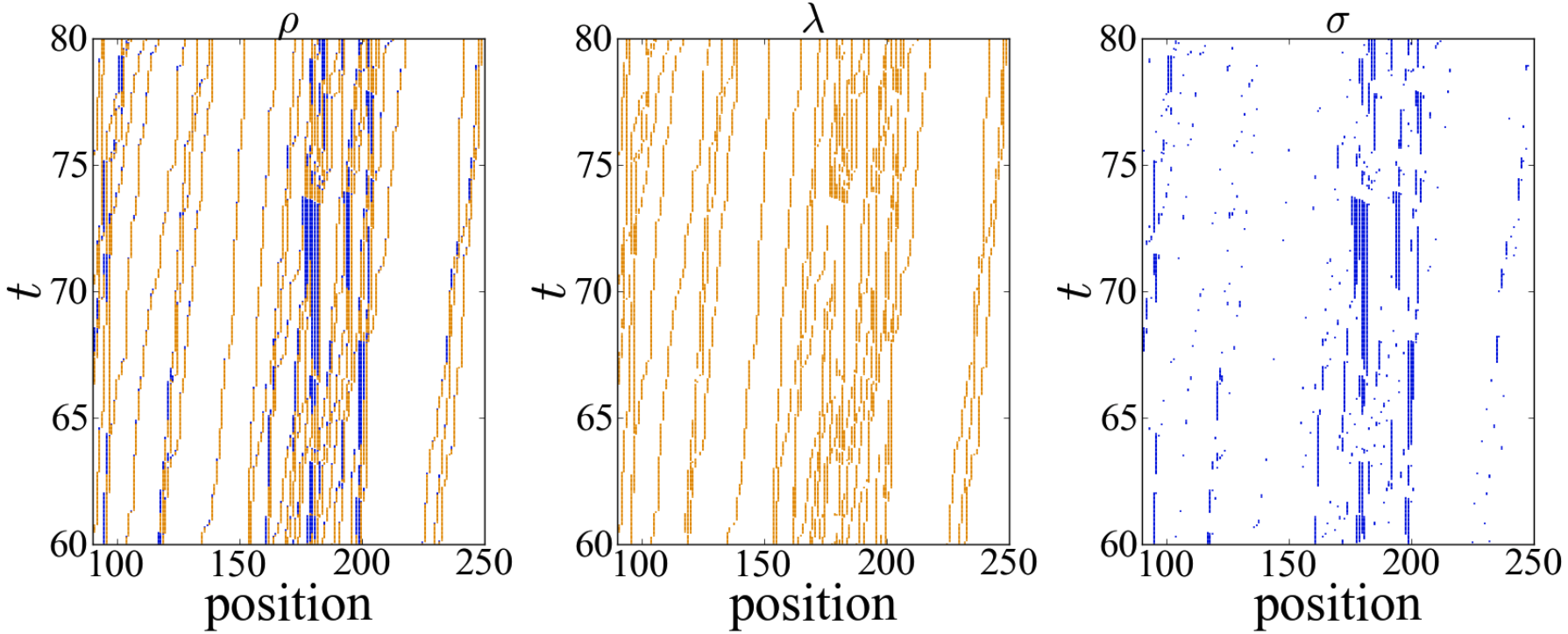
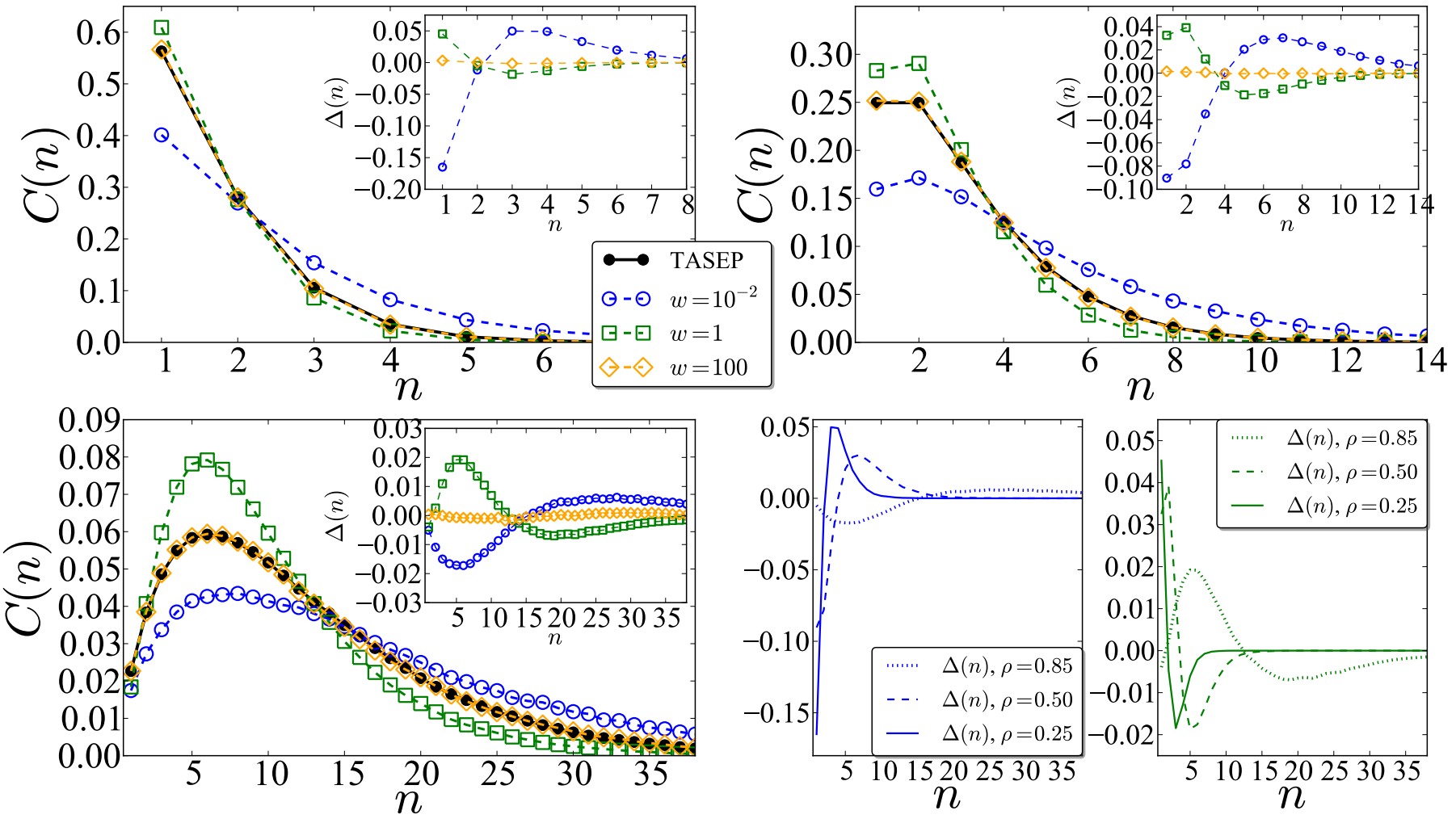


...and the presence of shocks in the density σ.

A more quantitative overview on the clustering

$C(n)$ = probability of finding a cluster of n particles

$\Delta(n)$ = difference between two-state model and TASEP



$(w = k/\gamma)$

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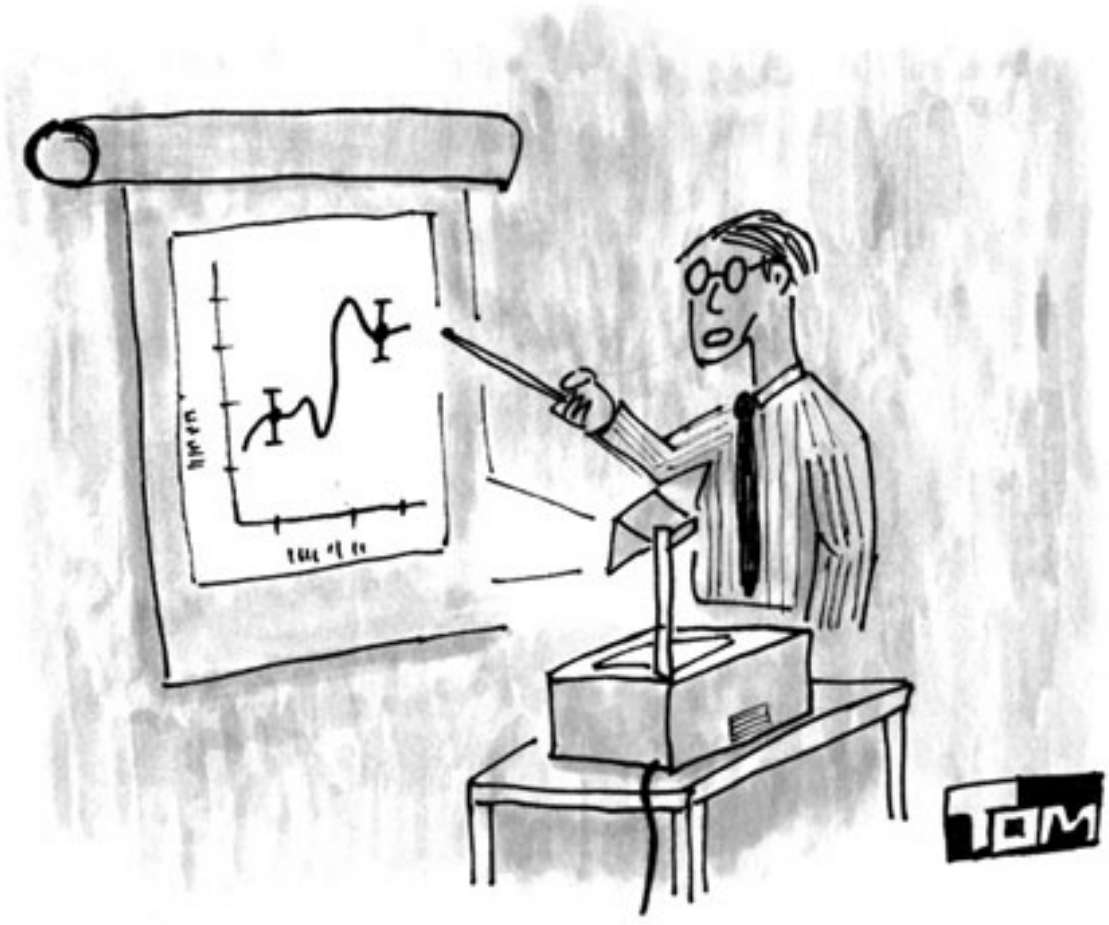

"WE CAN SEE HERE THAT THE AGREEMENT WITH THEORY IS EXCELLENT"

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Simulations of *S.cerevisiae* genome

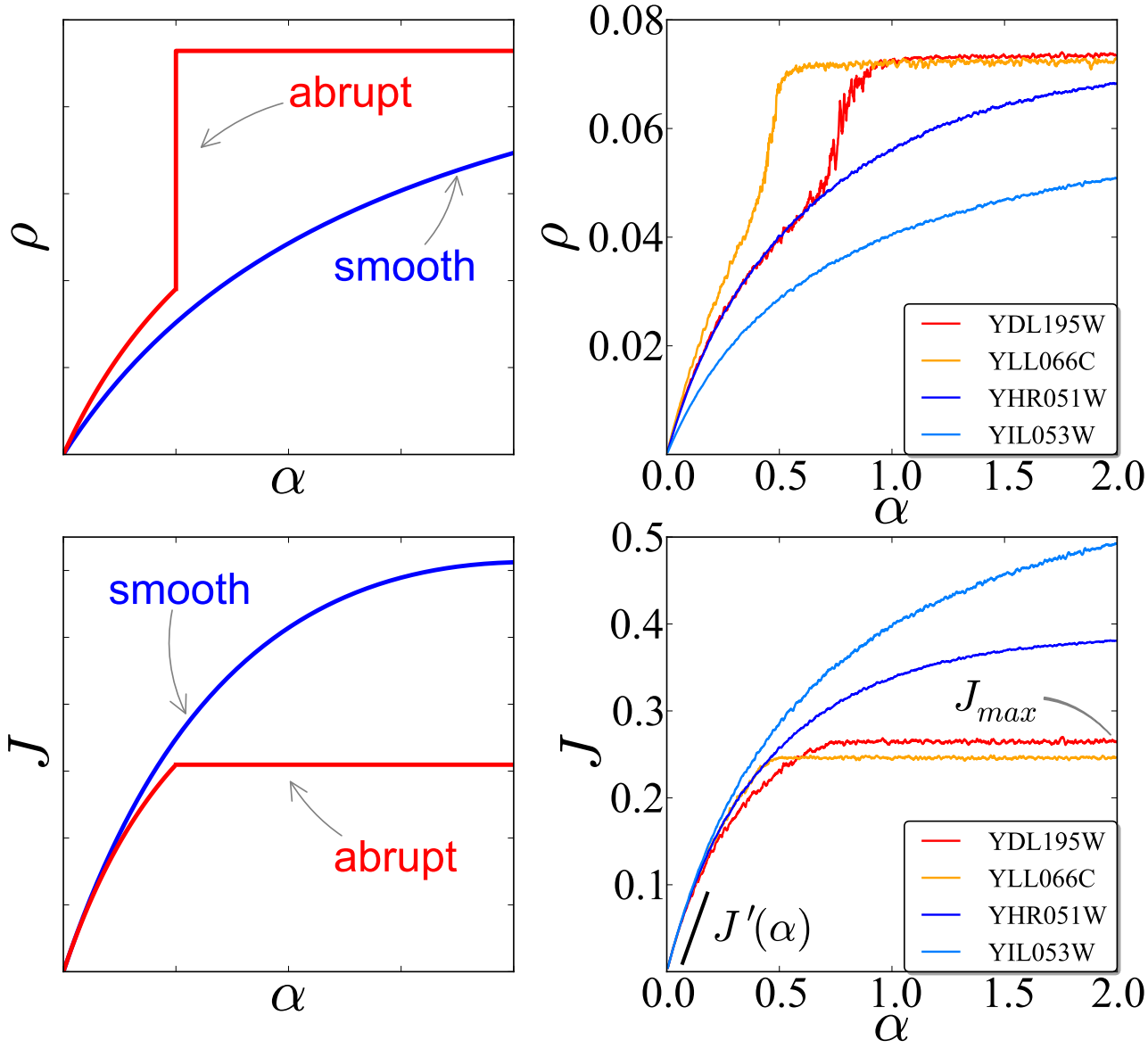
The final aim of this project is to predict the *transcriptome-proteome relation* and thereby to gain a deeper understanding of the physical and biological processes underlying translation.

We estimate all the necessary parameters (γ,$\{k_i\}$, β) and simulate the entire genome of *S.cerevisiae* ($\sim$ 6000 sequences). This allows us to:

- Classify the genes into two main types according to $\rho(\alpha)$ and $J(\alpha)$: significant correlation to biological functions.

- Estimate of the "operative" injection rates α for each mRNA (for the first time), which is experimentally not possible.

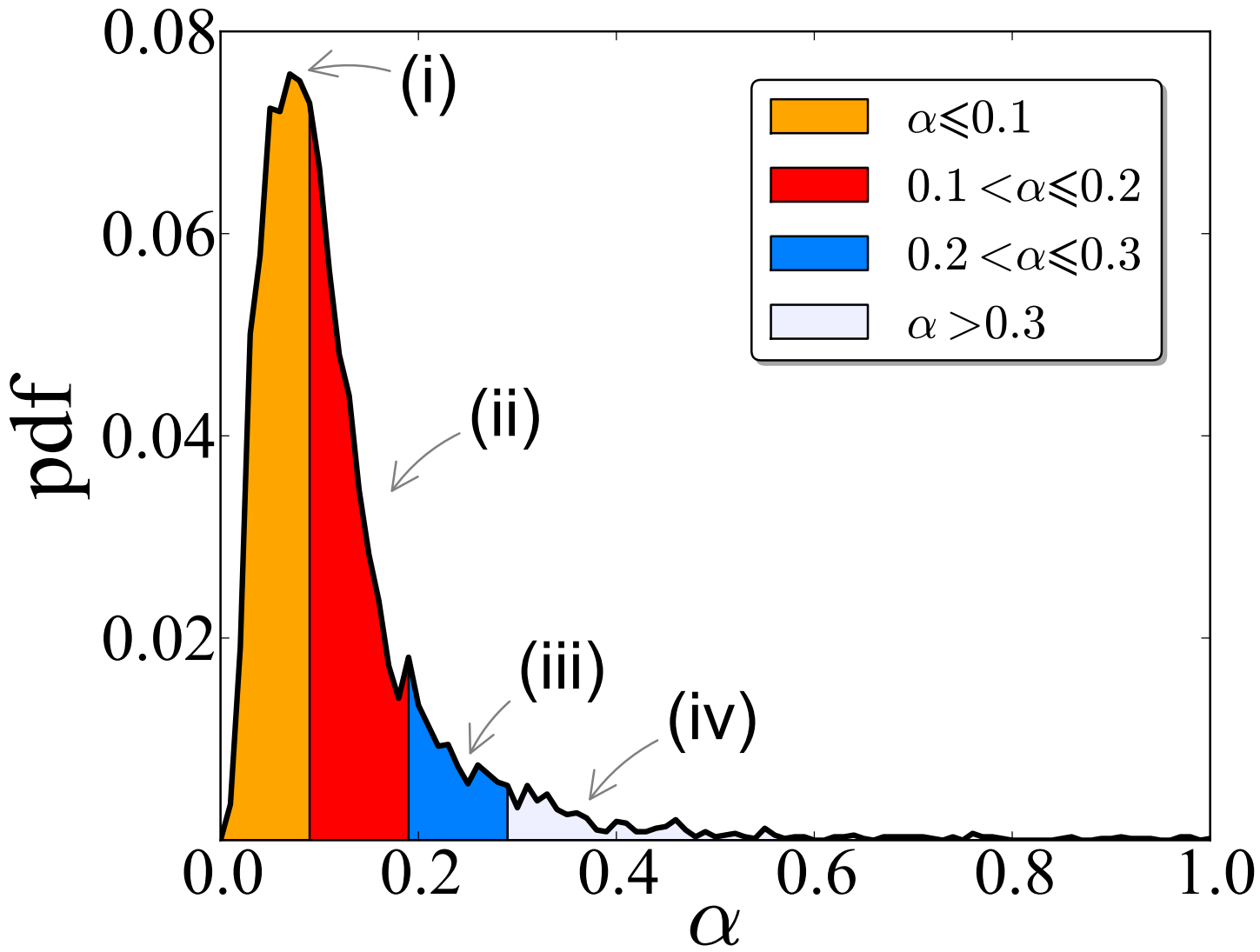
Classification of mRNA sequences in smooth/abrupt...



...and correlation with biological functions of encoded proteins.

L. Ciandrini, I. Stansfield, and M. C. Romano, *(to be submitted)*

Genome-wide estimates of α and biological functions



L. Ciandrini, I. Stansfield, and M. C. Romano, *(to be submitted)*

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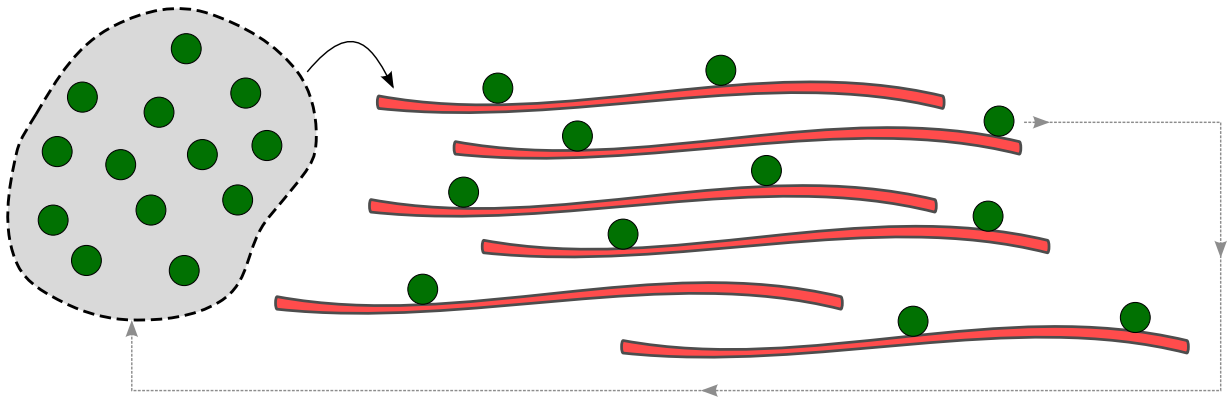
Conclusions...

To summarise, the two-state model condenses the particle's stepping cycle into two steps: internal transition (k) and translocation (γ).

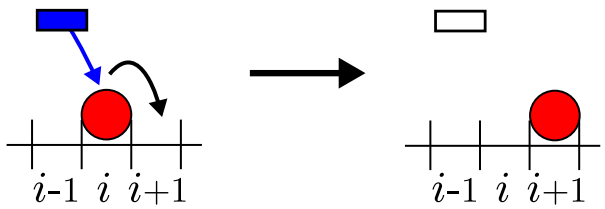
- The emerging dynamics substantially differs from the TASEP (e.g., no particle-hole symmetry, the phase diagram cannot be reproduced with effective rates, non-localised traffic jams);
- it recovers the TASEP in the limit $w \to \infty$ (but biologically $w \ll 1$);
- it allows direct application to genome-wide protein synthesis databases;
- the fundamental dynamics is also applicable to other biological processes (e.g., molecular motors).

...and further developments

- Competition for resources:
  - A mixed population of competing TASEPs with a shared reservoir of particles, P Greulich†, L Ciandrini†, R J Allen*, M C Romano*, *submitted* [arXiv:1111.1775].



  - Multiple phase transitions in a system of exclusion processes with limited reservoirs of particles and fuel carriers, C A Brackley, L Ciandrini, M C Romano, *to be submitted*.



- Folding TASEP
  (*in preparation*, with F Turci, A Parmeggiani, E Pitard and M C Romano)

Acknowledgments

- **Modeling**

  - M. C. Romano

  ICSMB and IMS, University of Aberdeen

  - R. J. Allen and P. Greulich

  Physics department, University of Edinburgh

  - A. Parmeggiani

  Biological Physics and Systems Biology Team, DIMNP, University of Montpellier II

  - F. Turci and E. Pitard

  Laboratoire Charles Coulomb, University of Montpellier II

  - C. A. Brackley

  ICSMB, University of Aberdeen

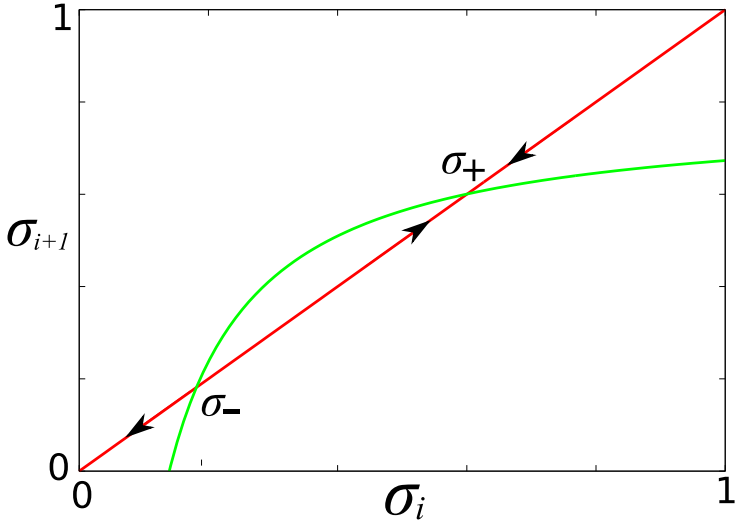
- **Experiments**

  - I. Stansfield and R. Betney

  Institute of Medical Sciences, University of Aberdeen

Thank you!

We find the general term of the recursion: $\sigma_i = \sigma_i(\sigma_1, J)$



$$\sigma_{i+1} = 1 - J(\frac{1}{k} + \frac{1}{\gamma\sigma_i})$$

which fixed points are

$$\sigma_\pm = \frac{1}{2}\left[(1 - \frac{J}{k}) \pm \sqrt{(1 - \frac{J}{k})^2 - \frac{4J}{\gamma}}\right] .$$

The general term is given by:

$$\sigma_i = \frac{-\sigma_-\sigma_+(\sigma_+^{i-1} - \sigma_-^{i-1}) + \sigma_1(\sigma_+^i - \sigma_-^i)}{-\sigma_-\sigma_+(\sigma_+^{i-2} - \sigma_-^{i-2}) + \sigma_1(\sigma_+^{i-1} - \sigma_-^{i-1})} .$$

Reasoning on the iterative map [B. Derrida, E. Domany, and D. Mukamel, *Journal of Statistical Physics*, 69(3-4):667–687, 1992] we are able to obtain the MF solutions

Low Density (LD) phase $[\alpha < \beta \ , \ \alpha \leqslant k(\sqrt{1+\gamma/k}-1)]$

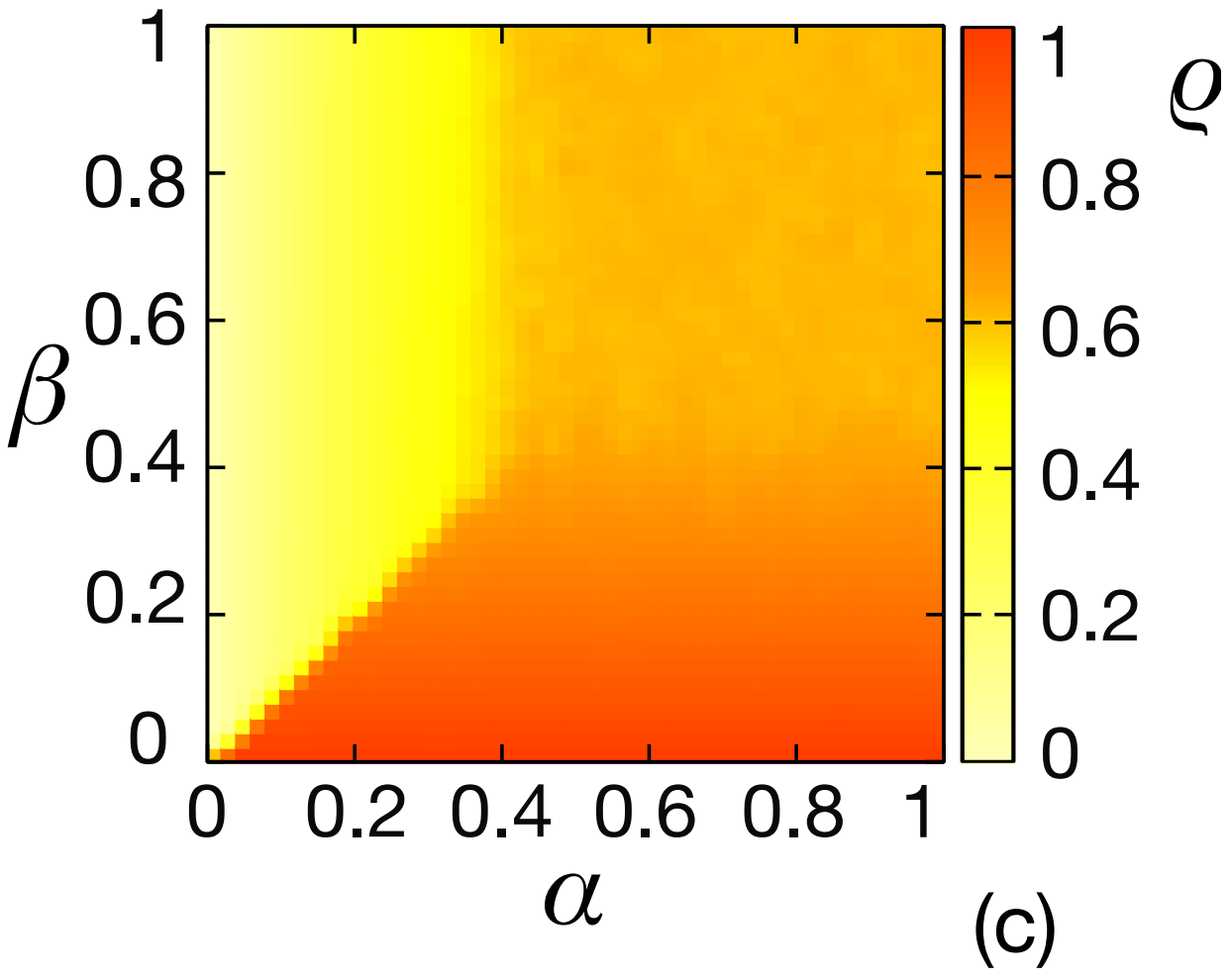
$$\rho = \frac{\alpha(k+\gamma)}{\gamma(k+\alpha)} \ , \qquad J = \alpha\frac{k(\gamma-\alpha)}{\gamma(k+\alpha)}$$

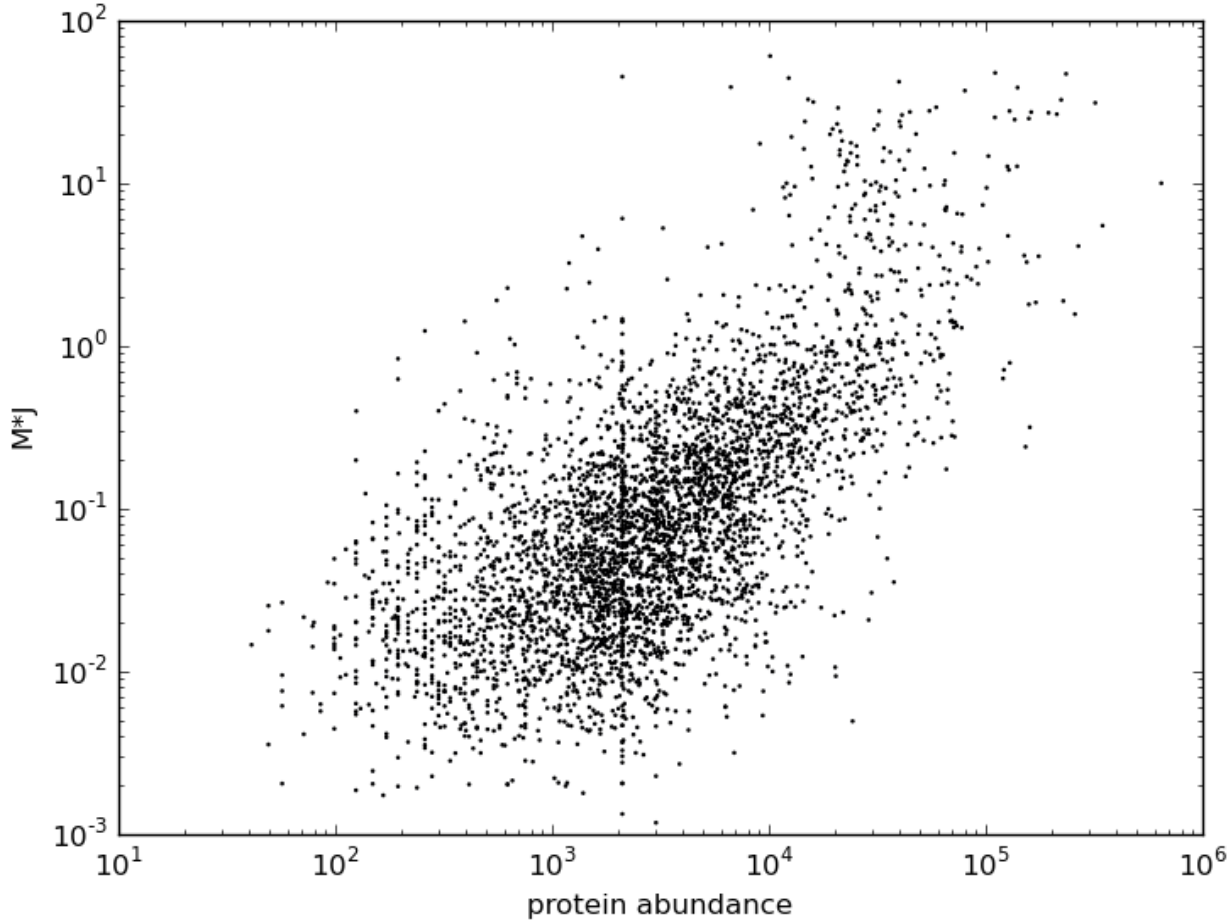
High Density (HD) phase $[\beta < \alpha \ , \ \beta \leqslant k(\sqrt{1+\gamma/k}-1)]$

$$\rho = 1 - \frac{\beta}{\gamma} \ , \qquad J = \beta\frac{k(\gamma-\beta)}{\gamma(k+\beta)}$$

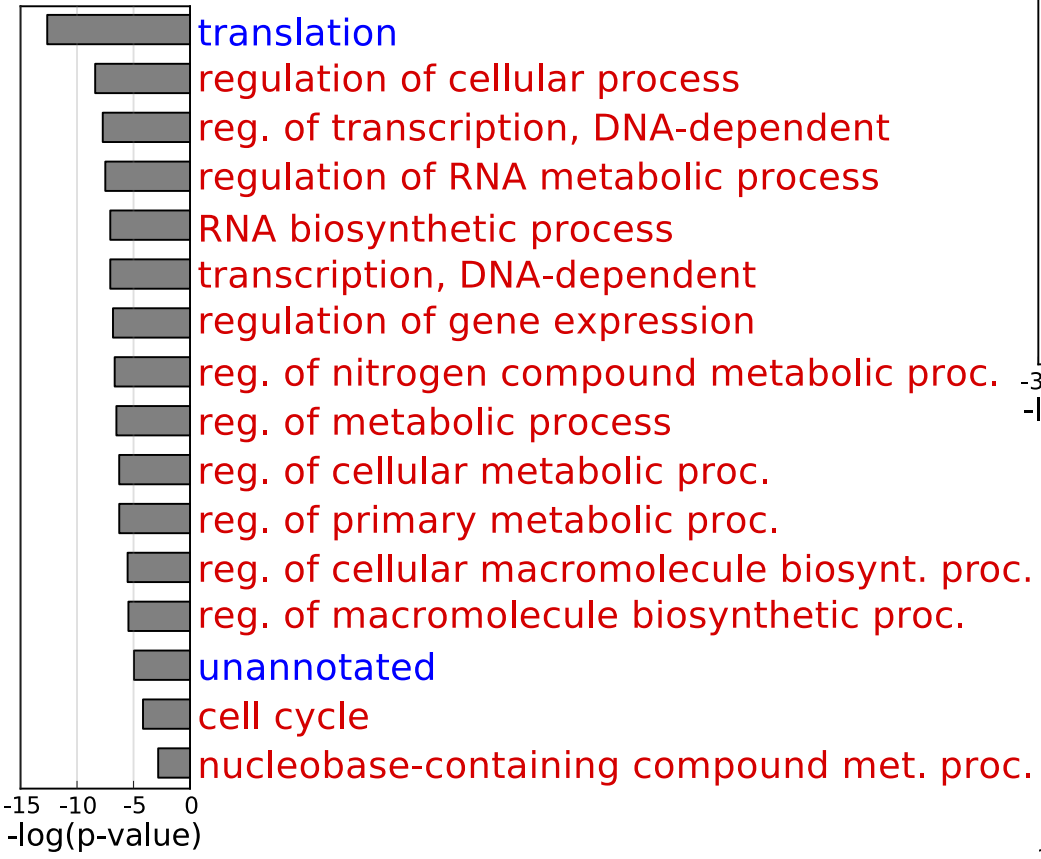
Maximal Current (MC) phase $[\alpha, \beta > k(\sqrt{1+\gamma/k}-1)]$

$$\rho = 1 - \frac{k}{\gamma}\left(\sqrt{1+\gamma/k}-1\right) \ , \qquad J = k\left[1 - 2\frac{k}{\gamma}\left(\sqrt{1+\gamma/k}-1\right)\right]$$

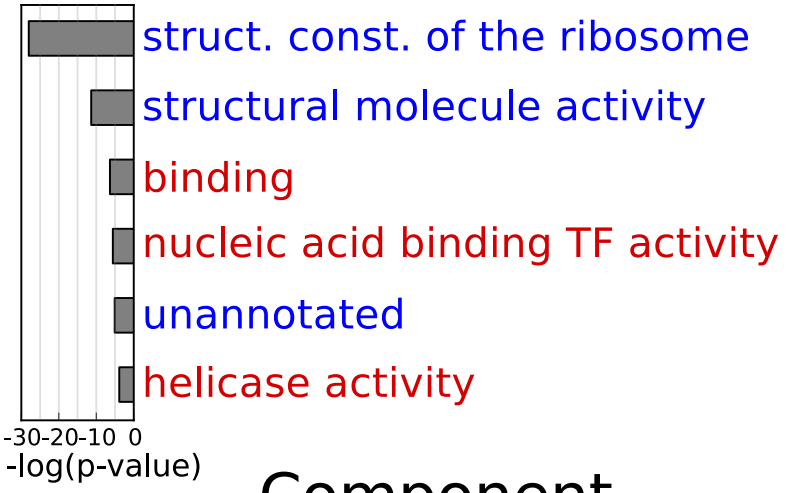
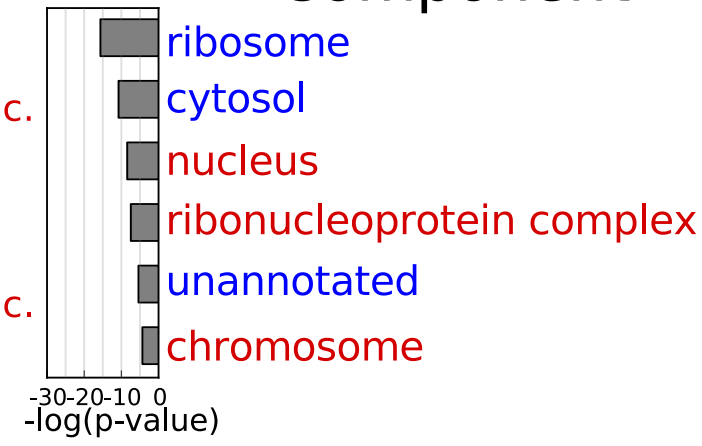

1
0.8
0.6
0.4
0.2
0
β
0
0.2
0.4
0.6
0.8
1
α
1
0.8
0.6
0.4
0.2
0
ϱ
(c)


10^2
10^1
10^0
10^{-1}
10^{-2}
10^{-3}
[M*]
10^1
10^2
10^3
10^4
10^5
10^6
protein abundance

Process



Function



Component