# Regulation of Motor Traffic and Control of Noisy Gene Expression: Roles of Signals, Sequence, Structure and Suppressors in Decoding and Recoding

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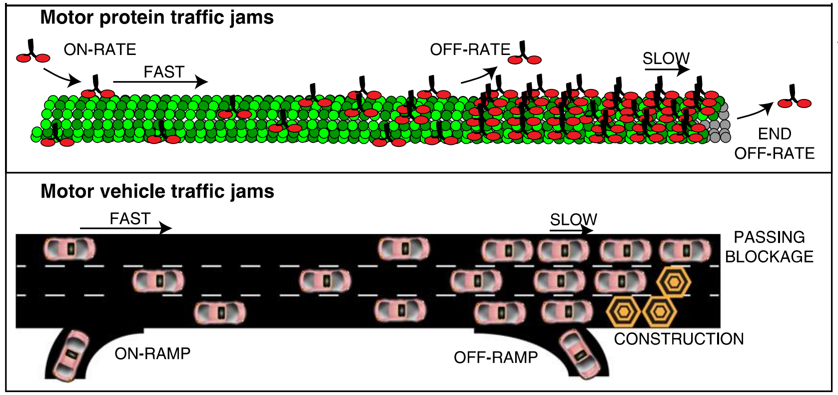
Home page: http://home.iitk.ac.in/~debch/profile_DC.html
Alternative Home page: https://sites.google.com/site/debchphy/

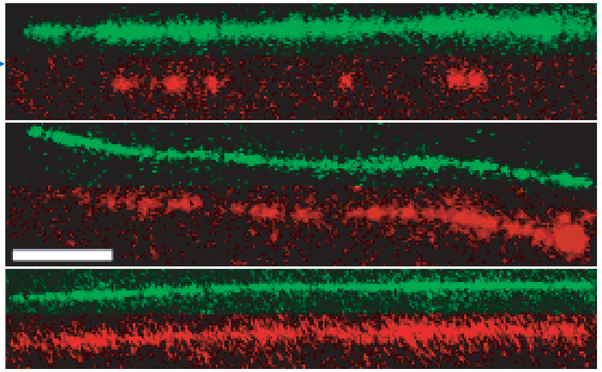



J.L. Ross, PNAS (2012)

Traffic of molecular motors on MT track

MCAK

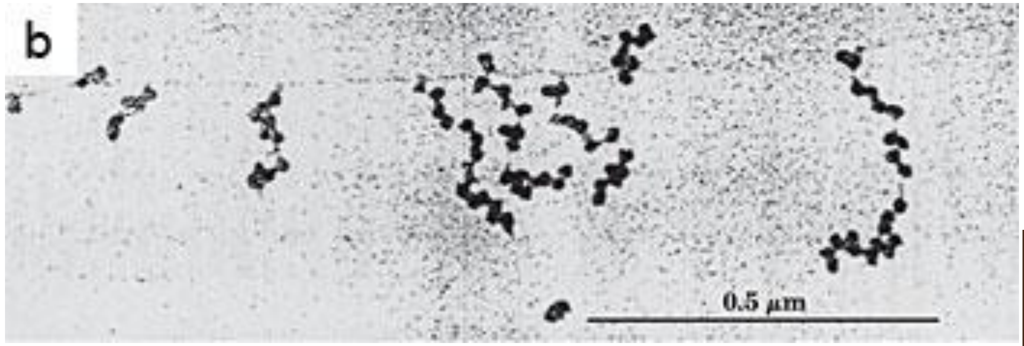
KIF1A



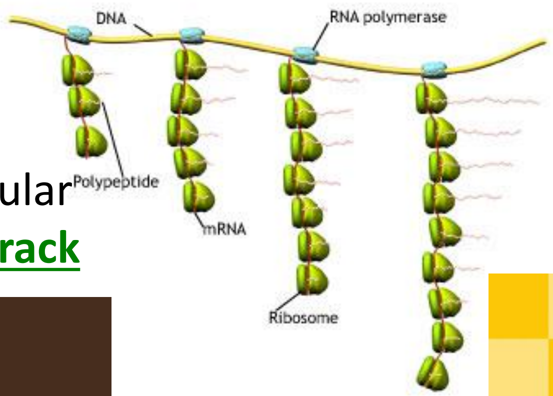
Nishinari, Okada, Schadschneider, Chowdhury. Phys. Rev. Lett (2005)

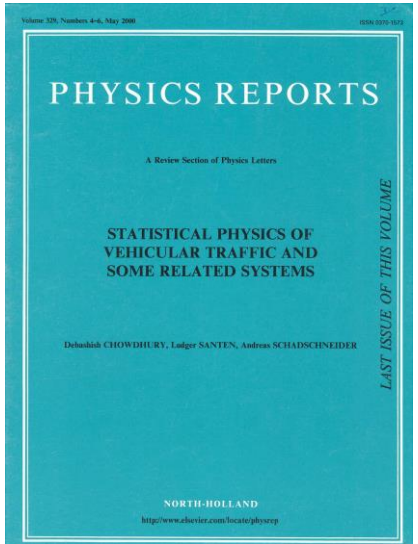
**Non-equilibrium STEADY-STATE**

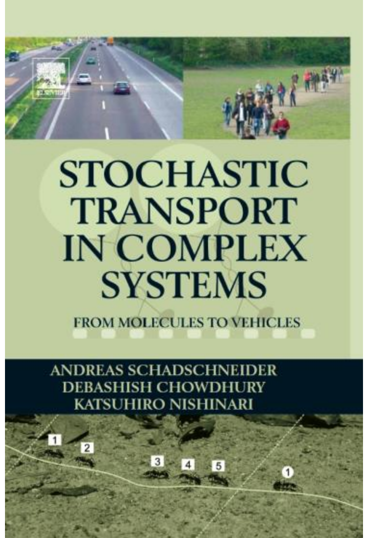
**NO underlying HAMILTONIAN, NO equilibrium exists!!**

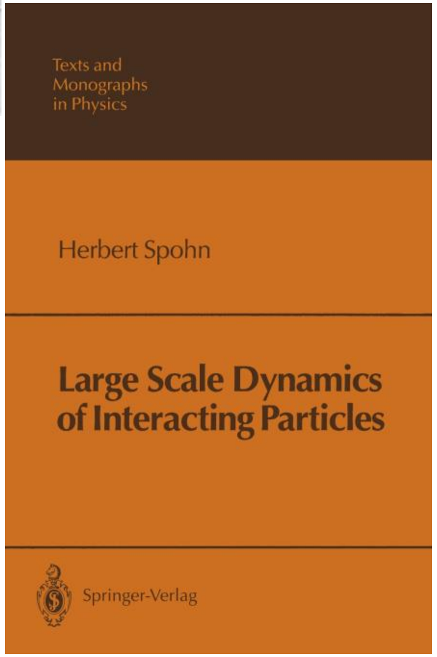


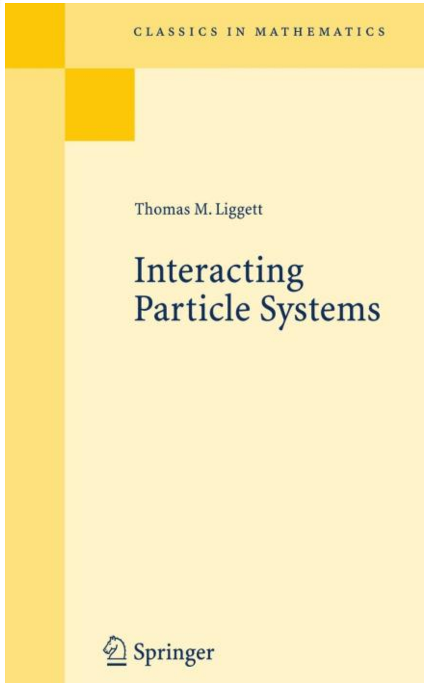

Traffic of molecular motors on NA track



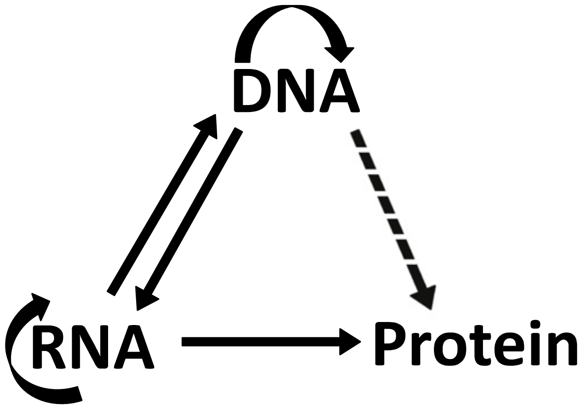



| Machine | Template | Product | Function |
|---|---|---|---|
| DdRP | DNA | RNA | Transcription |
| DdDP | DNA | DNA | DNA replication |
| RdRP | RNA | RNA | RNA replication |
| RdDP | RNA | DNA | Reverse transcription |
| Ribosome | mRNA | Protein | Translation |




Central Dogma in Molecular Biology

Machine

**Template** → **Product**

A **motor** that moves along hetero-polymer track,

**decodes** genetic message,

**polymerizes** a hetero-polymer using another hetero-polymer template.

## Molecular Traffic Jams on DNA

Ilya J. Finkelstein[1,2] and Eric C. Greene[3,4]

Annu. Rev. Biophys (2013)

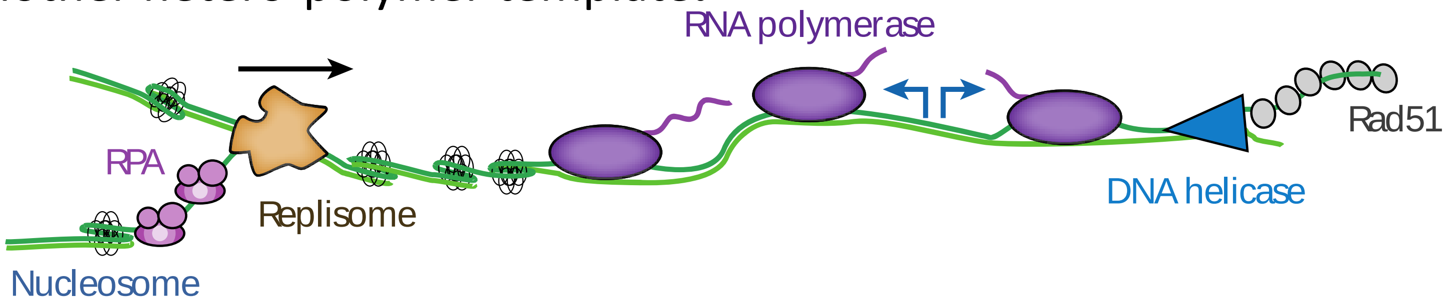
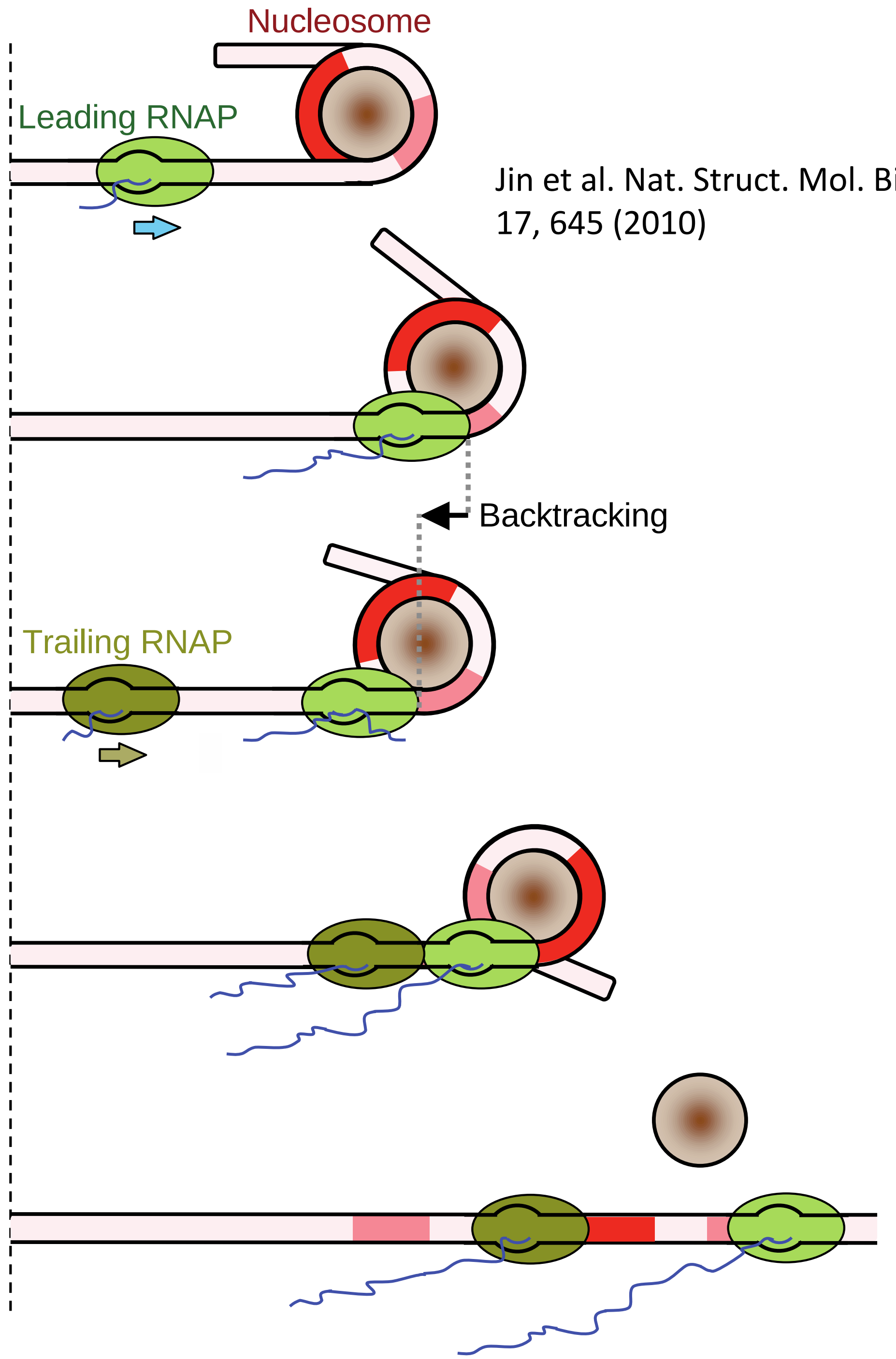



Figure 1

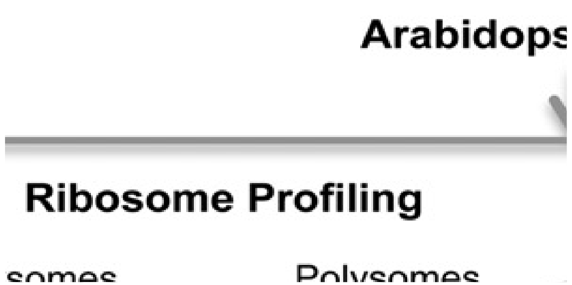
DNA replication, transcription, and repair must occur simultaneously on a crowded nucleic acid substrate. Conflicts between these molecular machines must be resolved rapidly to maintain cell viability and to avoid genomic instability.

# Beneficial effects of Traffic Congestion



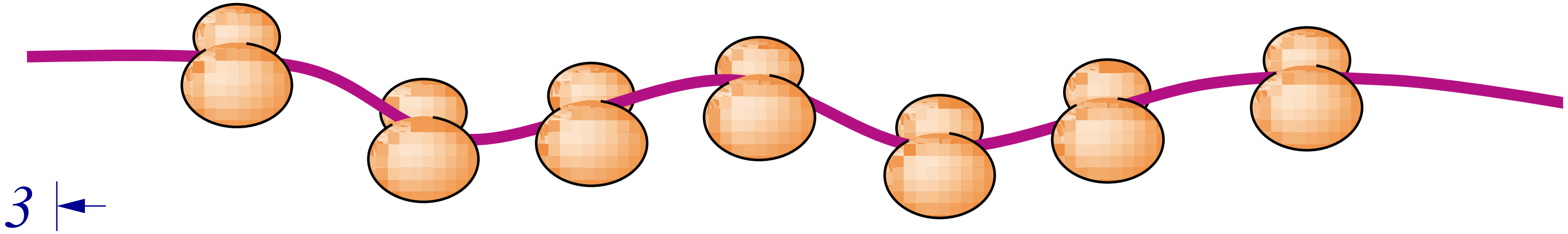

Jin et al. Nat. Struct. Mol. Biol. 17, 645 (2010)

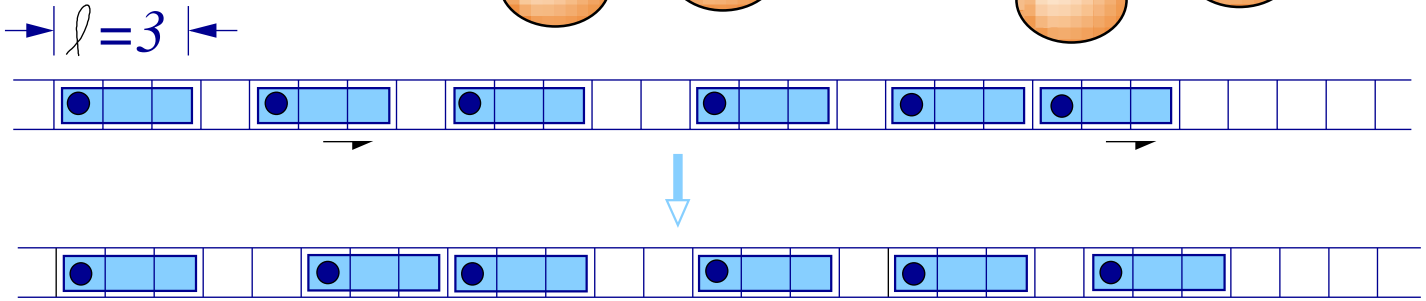
Following RNAP can push the leading stalled RNAP assisting it in dislodging the nucleosome proteins thereby resuming Transcription.




Juntawong et al. PNAS (2014)

**Polysome: Ribosome Traffic on a single mRNA**



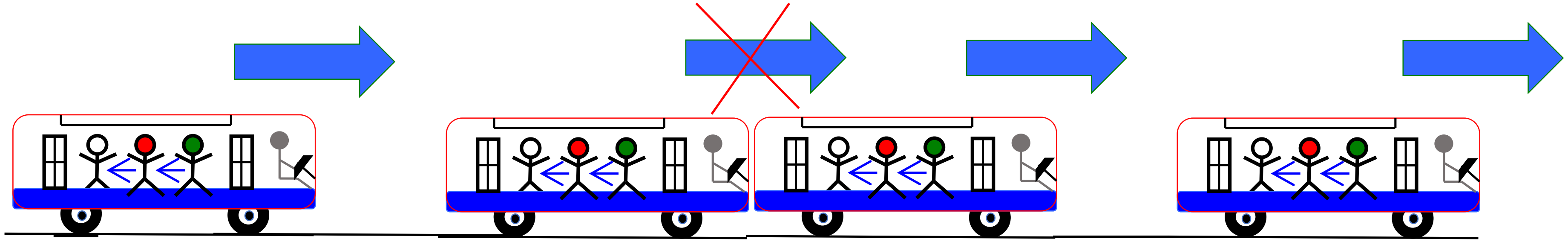



TASEP for Hard Rods

**Kinetics of biopolymerization on nucleic acid templates**

Carolyn T. MacDonald, Julian H. Gibbs, Allen C. Pipkin

Biopolymers, Volume 6, Issue 1 January 1968 Pages 1–25



**Polysome: Ribosome Traffic on a single mRNA**

Basu & Chowdhury, Phys. Rev. E (2007)

Garai, Chowdhury, Chowdhury, Ramakrishnan, Phys. Rev. E (2009)

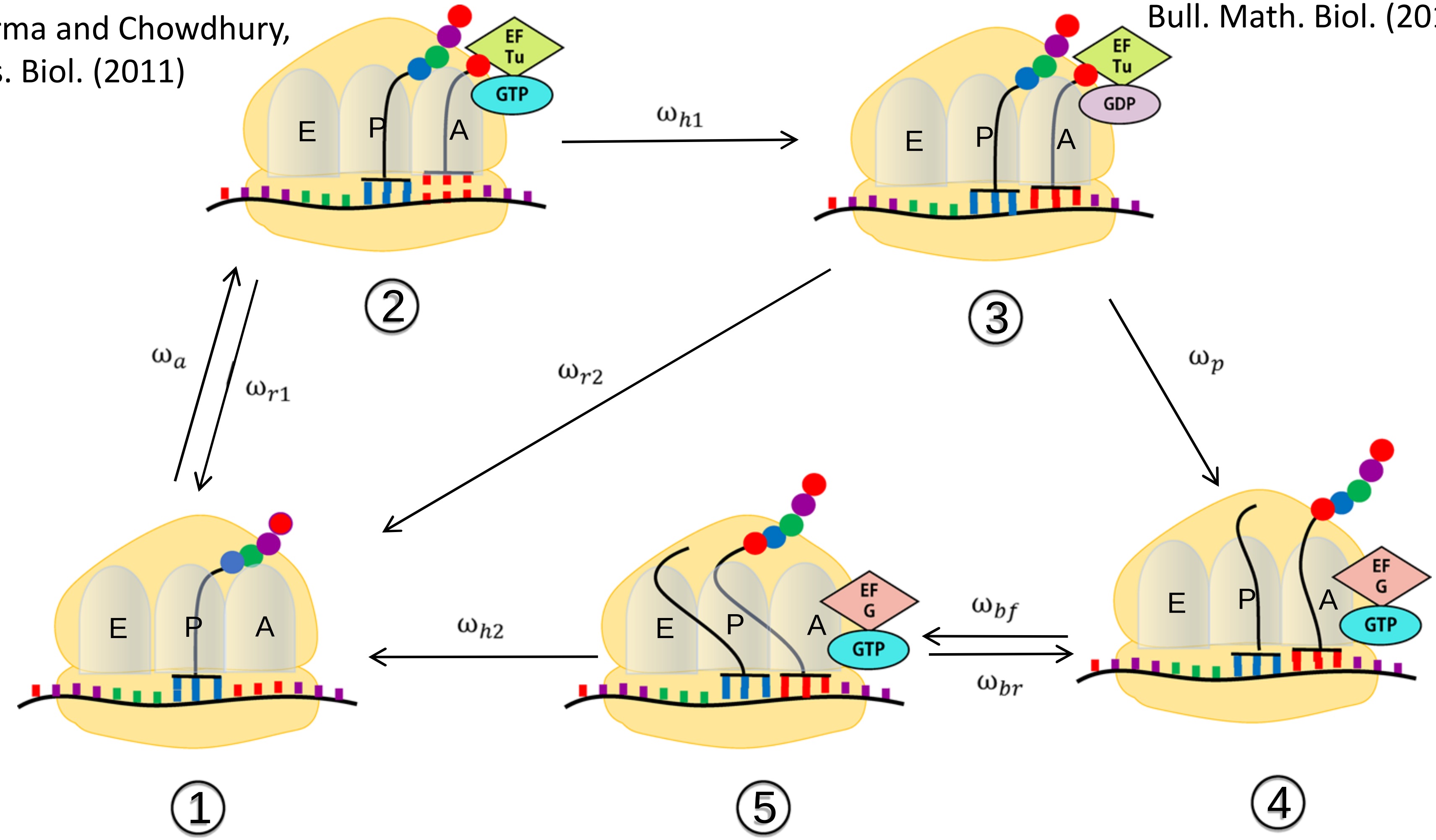
Sharma & Chowdhury, J. Theor. Biol. (2011)

The discrete mechano-chemical states of the machine form the vertices of a ***network (graph)*** while the directed edges denote the allowed transitions.

Machine operation, i.e., its stochastic kinetics, is modeled as a ***Markov process*** in a heat bath at a constant temperature and it is formulated in terms of ***master equations***.

Dutta and Chowdhury, Bull. Math. Biol. (2017)

Sharma and Chowdhury, Phys. Biol. (2011)

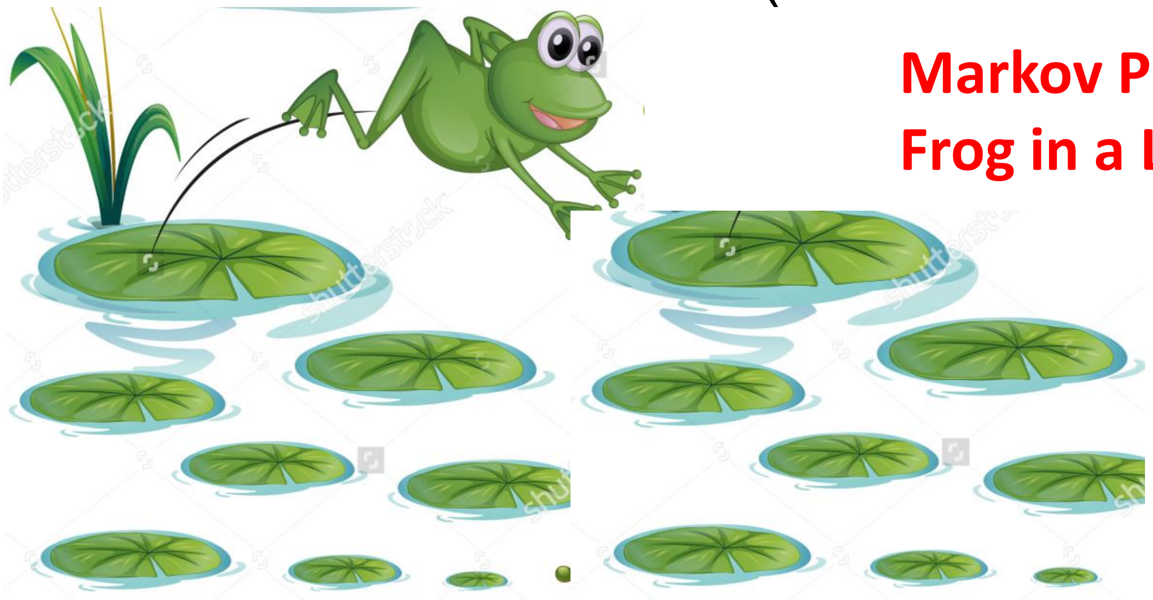


# **Master equation**: general form for "***States and Rates***"

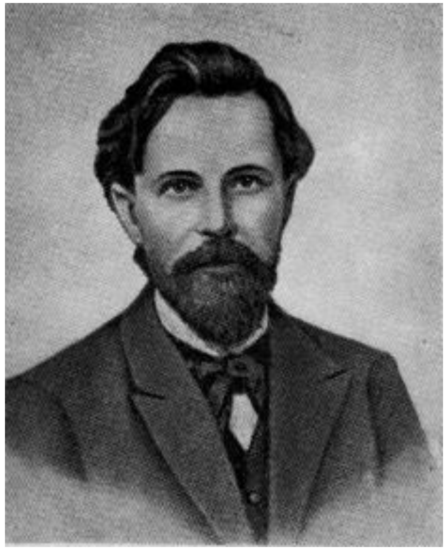
$P_n(t)$ = Probability of finding the "particle" in the discrete state n at time t.

$$\frac{dP_n(t)}{dt} = \underbrace{\sum_m P_m(t)\, W(m \to n)}_{\text{GAIN terms}} - \underbrace{\sum_{m'} P_n(t)\, W(n \to m')}_{\text{Loss terms}}$$

$W(n \to m)$ = Probability of transition $n \to m$ per unit time ("rate constant").



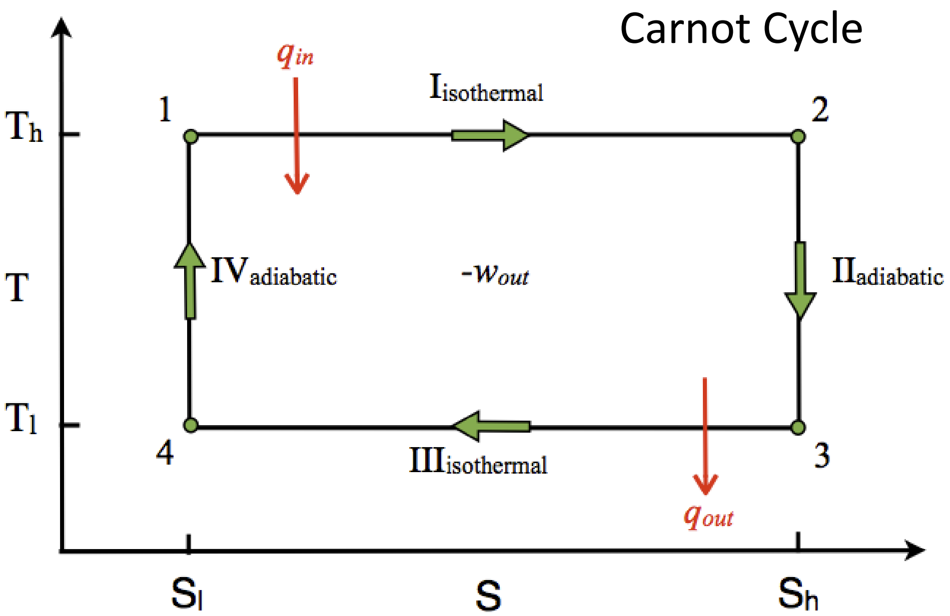
**Markov Process: Frog in a Lily Pond**



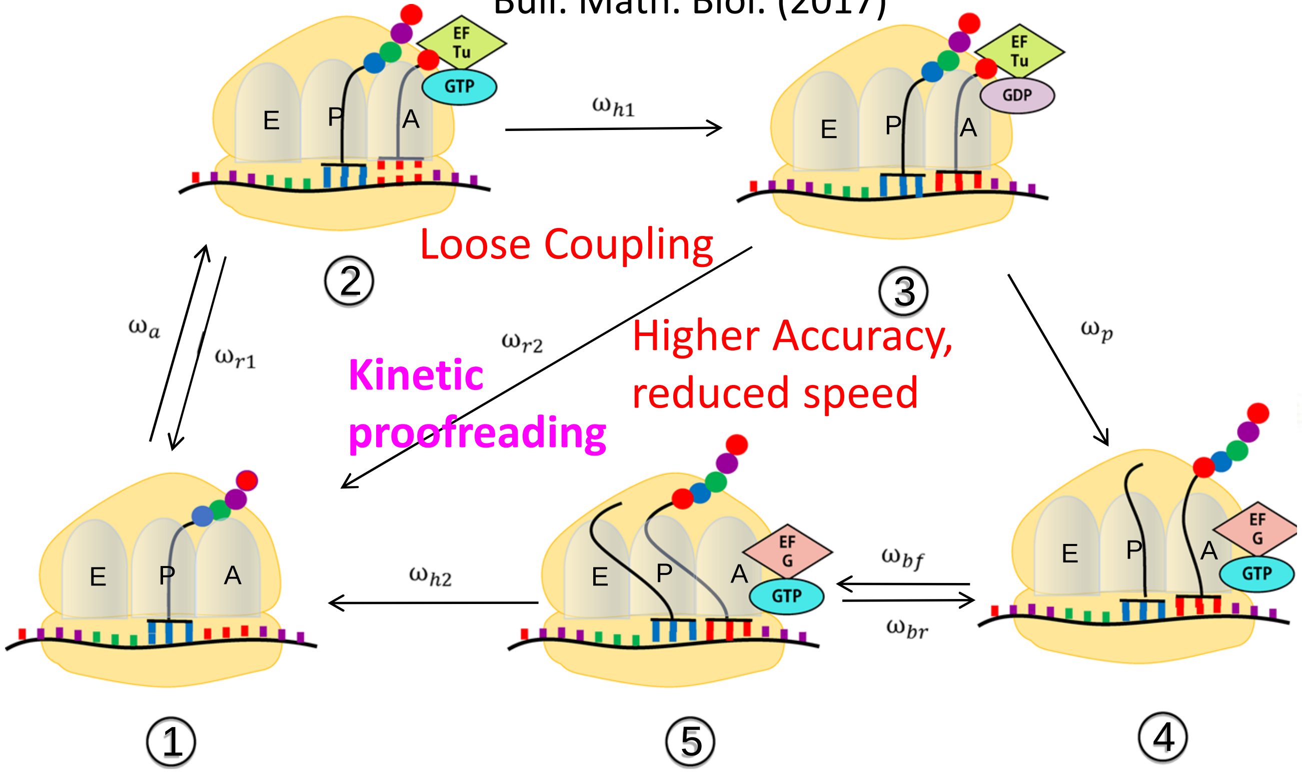
A. A. Markov

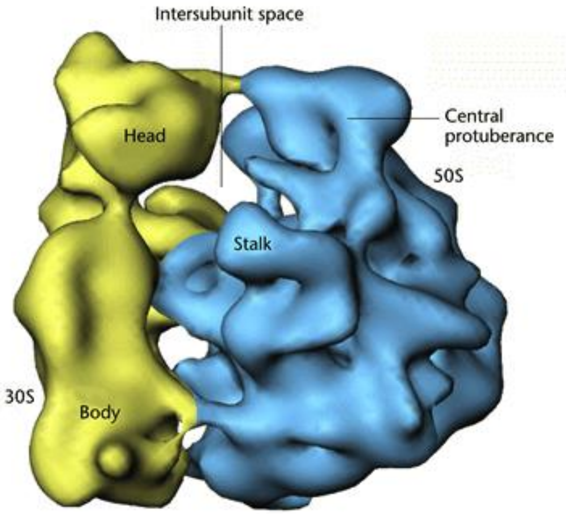
Sadi Carnot (1796-1832)

Source: wikipedia




Dutta and Chowdhury, Bull. Math. Biol. (2017)



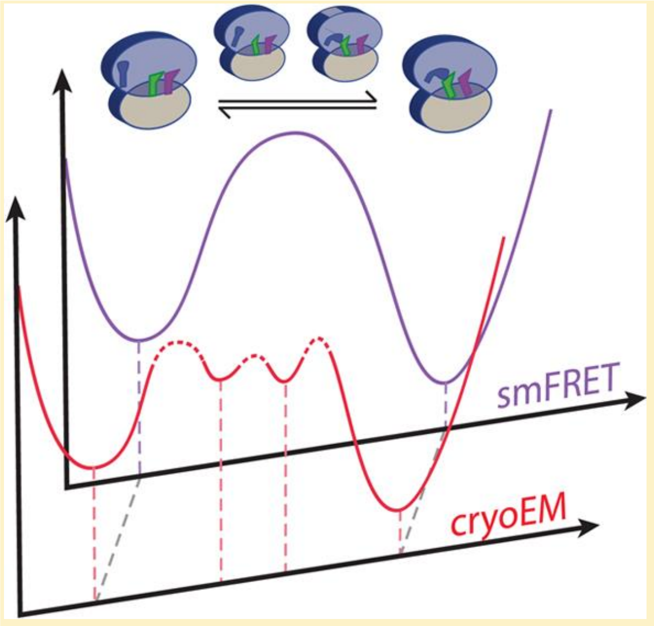




Ribosome

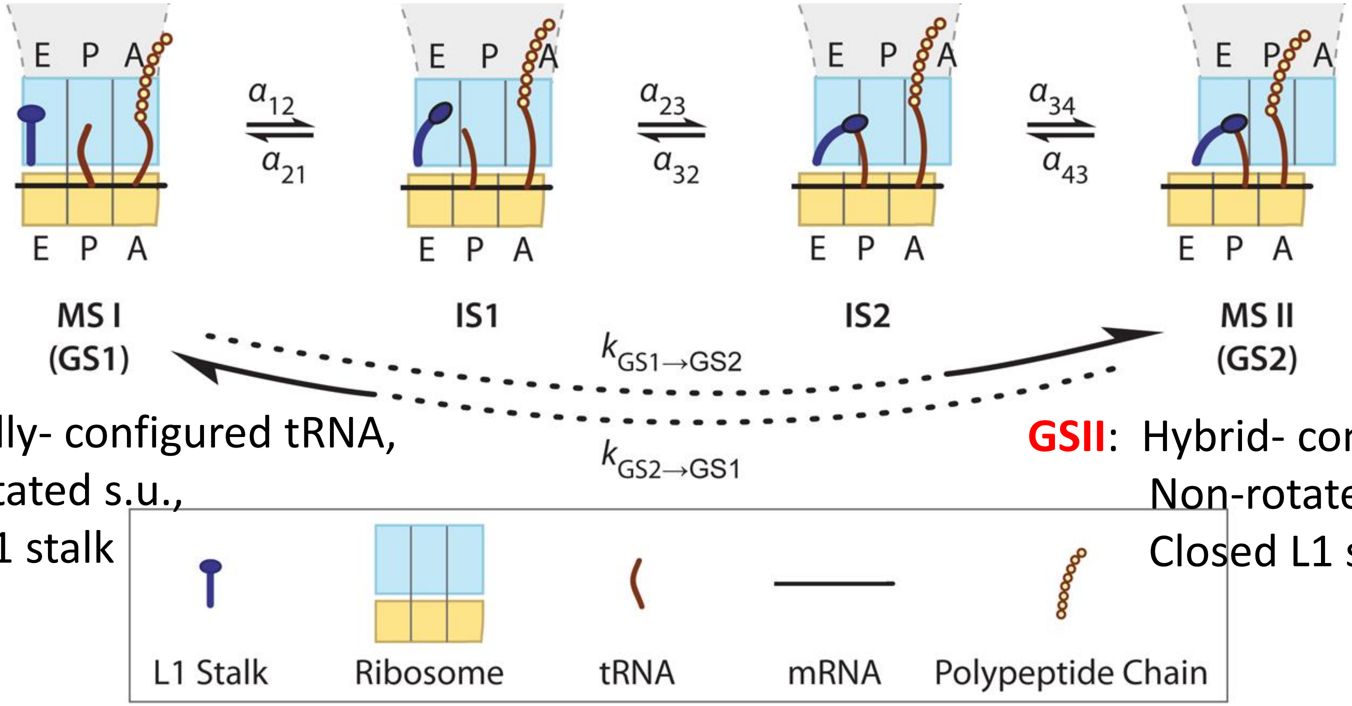
# Quantitative Connection between Ensemble Thermodynamics and Single-Molecule Kinetics: A Case Study Using Cryogenic Electron Microscopy and Single-Molecule Fluorescence Resonance Energy Transfer Investigations of the Ribosome

Colin D. Kinz-Thompson,[†,∥] Ajeet K. Sharma,[‡,∥,¶] Joachim Frank,[⊥,§] Ruben L. Gonzalez, Jr.,[†]
and Debashish Chowdhury*,[‡]

THE JOURNAL OF PHYSICAL CHEMISTRY B



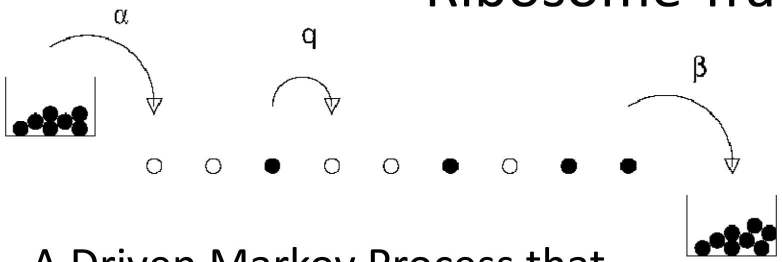

**Fluctuating kinetics of PRE until EF-G-catalyzed Translocation**



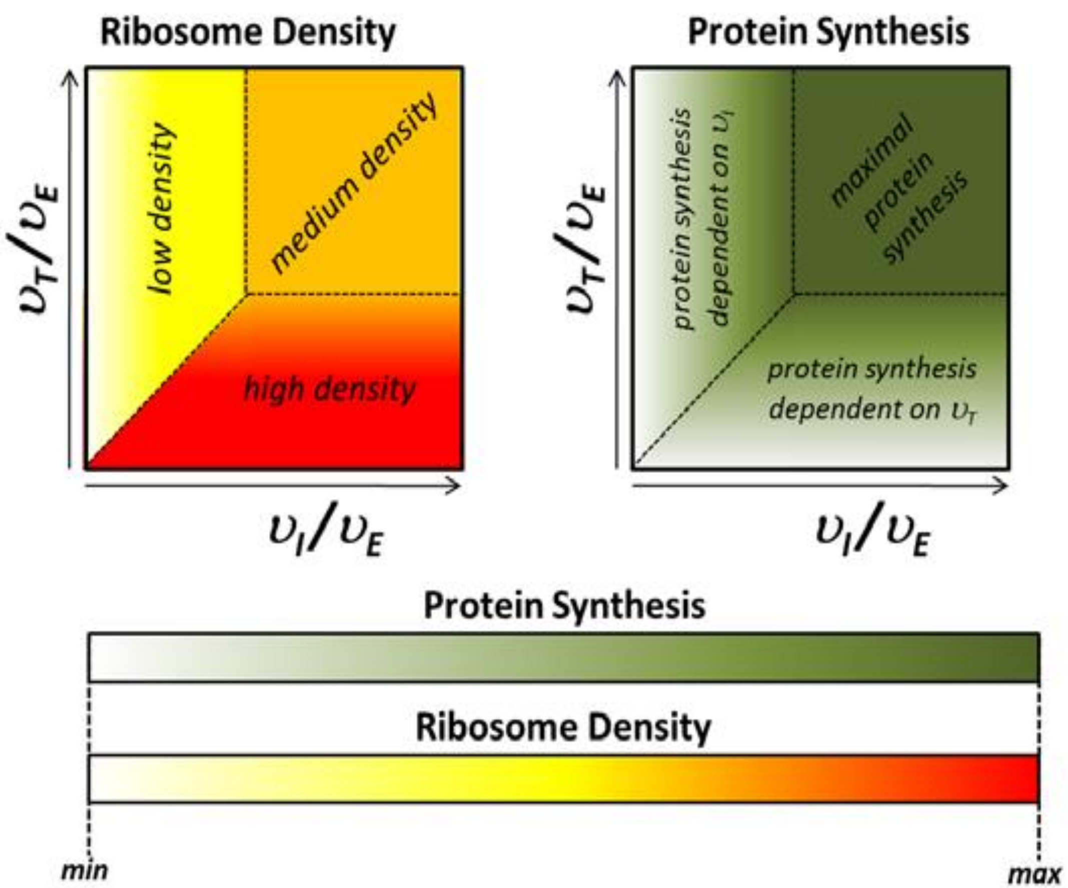

**GSI**: Classically- configured tRNA,
Non-rotated s.u.,
Open L1 stalk

**GSII**: Hybrid- configured tRNA,
Non-rotated s.u.,
Closed L1 stalk

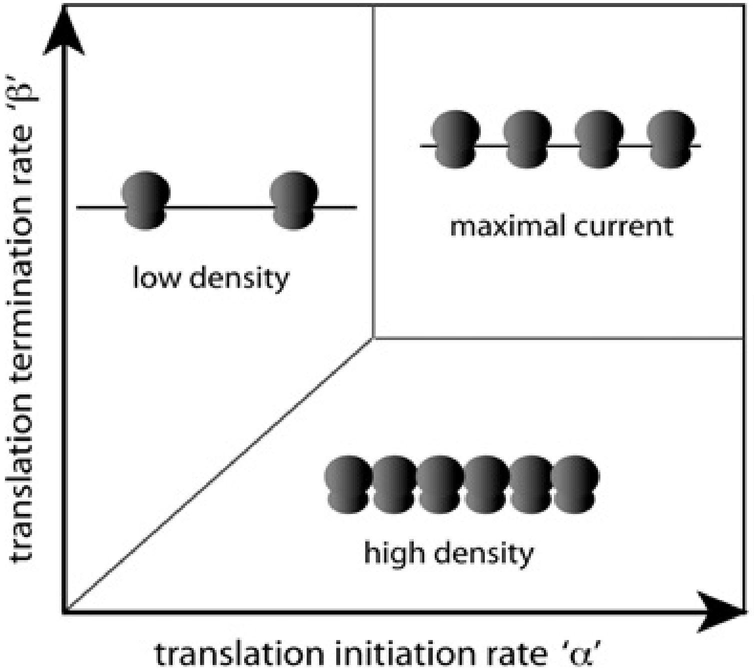
# Ribosome Traffic on a single MRNA




A Driven Markov Process that reaches NON-Eq Steady State (NESS).




**Figure' 4.' The' relationship' between' ribosome' density' and' protein' synthesis,**!as!predicted!by!*TASEP*!models.!The!left!panel!shows!ribosome! densities! as! a! function! of! different! ratios! of! $\upsilon_{I,\$}$ $\upsilon_{E}$! and! $\upsilon_T$! (initiation,! elongation! and! termination! rates)! under! the! standard! *TASEP*! assumptions! of! a! uniform! elongation! rate! and! of! unlimited! ribosome! supply.!The!right!panel!shows!the!corresponding!protein!synthesis!rates.!




Gorgoni et al. Biochem. Soc. Trans. 42, 160 (2014)

Von der Haar, Comp. & Struct. Biotech. J. (2012)

Spatio-temporal organization of Ribosomes on mRNA track
during Translation:
effects of mechano-chemical cycles of individual Ribosomes
on Polysomes

A. Basu and D. Chowdhury, Phys. Rev. E 75, 021902 (2007)

Garai, Chowdhury and Ramakrishnan, *Phys. Rev. E*, 79, 011916 (2009)

Garai, Chowdhury, Chowdhury and Ramakrishnan, Phys. Rev. E 80, 011908 (2009)

Sharma and Chowdhury, Phys. Rev. E, 82, 031912 (2010)

Sharma and Chowdhury, Physical Biology, 8, 026005 (2011).

Sharma and Chowdhury, Journal of Theoretical Biology, 289, 36 (2011).

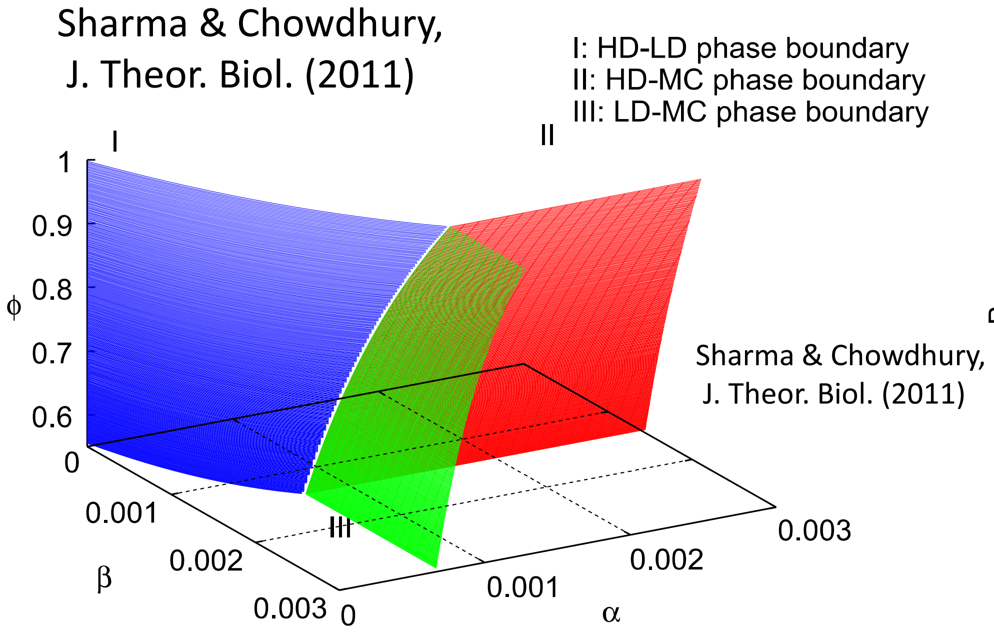



**Fig. 2.** Phase diagram of ribosome traffic model in the 3-dimensional space spanned by $\alpha,\beta$ and $\phi$.

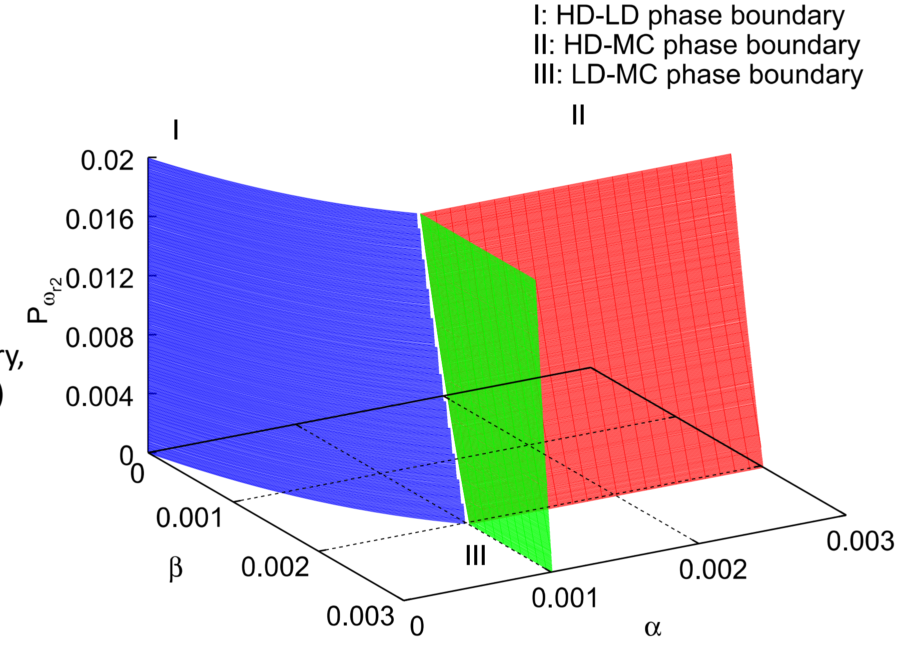



**Fig. 4.** Phase diagram of ribosome traffic model in the 3-dimensional space spanned by $\alpha,\beta$ and $P_{\omega_{r2}}$.

Regulation of Ribosome Traffic on mRNA template and

Control of Unconventional Translation:

Consequences of Programmed Error and Recoding

*"Unlike DNA, which universally adopts a double helical conformation, RNA has extensive intramolecular interactions that cause it to fold into an array of complex structures. RNA structure is highly dynamic and is governed by factors such as temperature, cellular energy state, ……. RNA structures enable a myriad of functions, which include encoding genetic information….."*

Lewis et al., Nat. Rev. Mol. Cell Biol. (2017).

Review CellPress

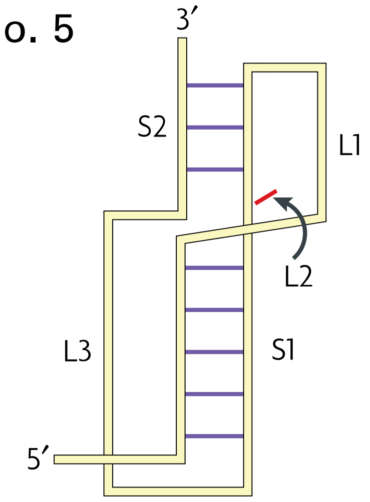
**Gene regulation by structured mRNA elements**

**Andreas Wachter** Trends in Genetics, May 2014, Vol. 30, No. 5

Viral RNA pseudoknots: versatile motifs in gene expression and replication

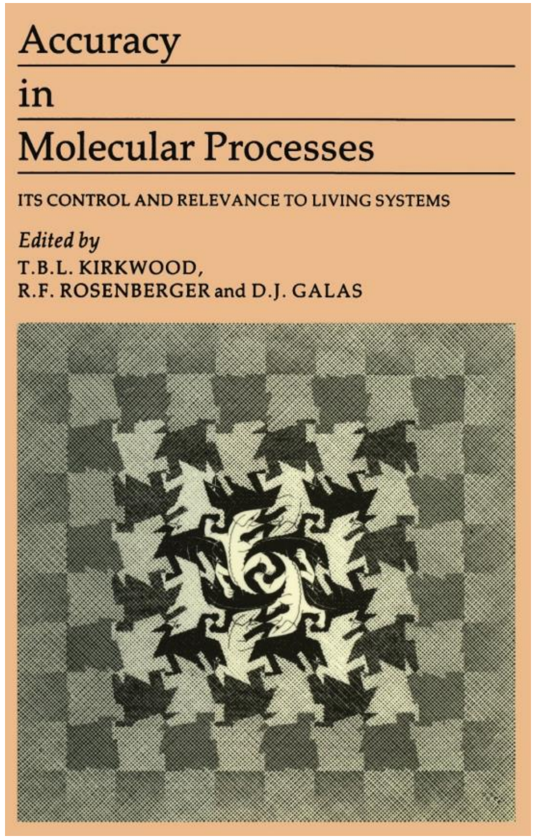
*Ian Brierley*, Simon Pennell‡ and Robert J. C. Gilbert§*

www.nature.com/reviews/micro AUGUST 2007 | VOLUME 5



H-type pseudoknot

Next we explore the regulatory roles of the secondary structures of mRNA on Ribosome Traffic




# Fidelity and infidelity

**Miroslav Radman** Nature, 413, 115 (2001)

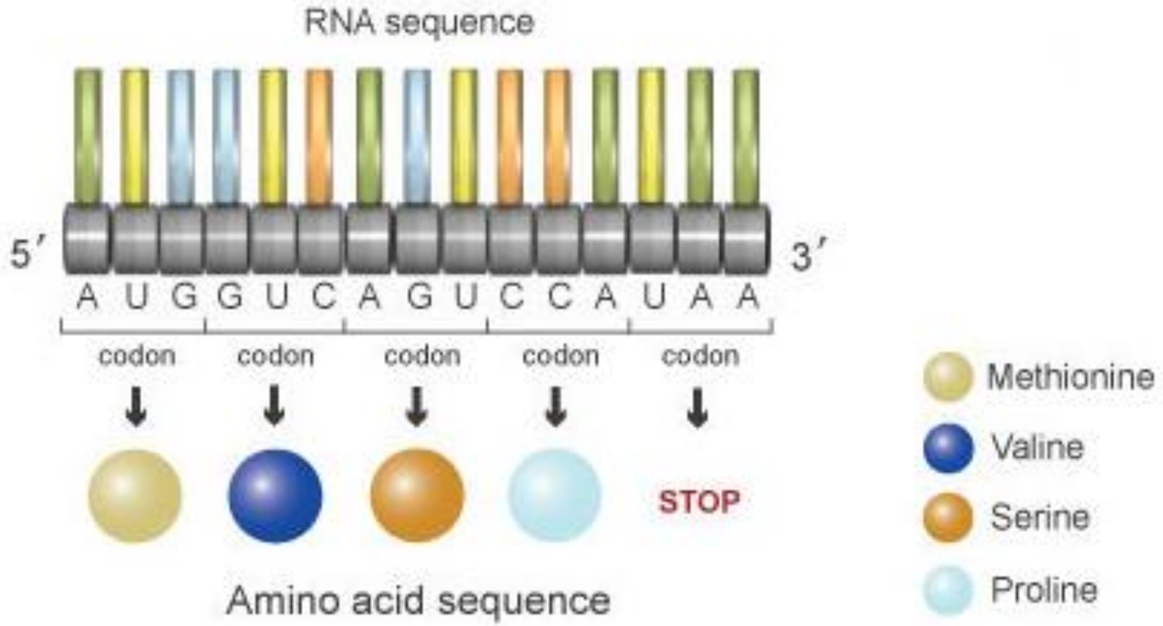
"Nature does not exhaust itself for the sake of fidelity and perfectionism. Rather, errors are made, often repaired or discarded, but always tested as the source of blind innovation during the continuous adaptation to unpredictable environmental changes and challenges."

Molecular evolution

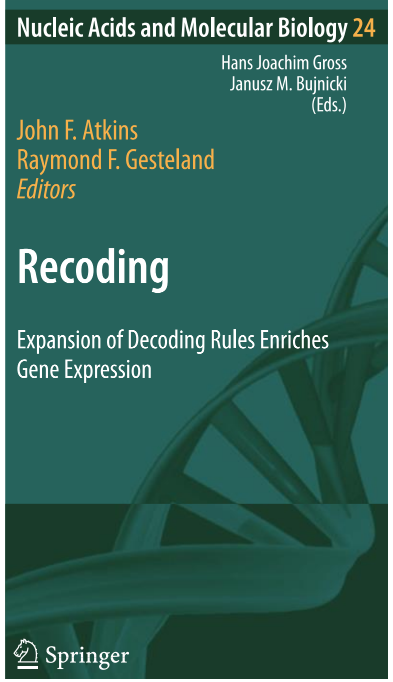
*Errors and infidelity, even wastefulness, can cause individual failure, but they are also a source of innovation and robustness, ensuring the perpetuation of life.*

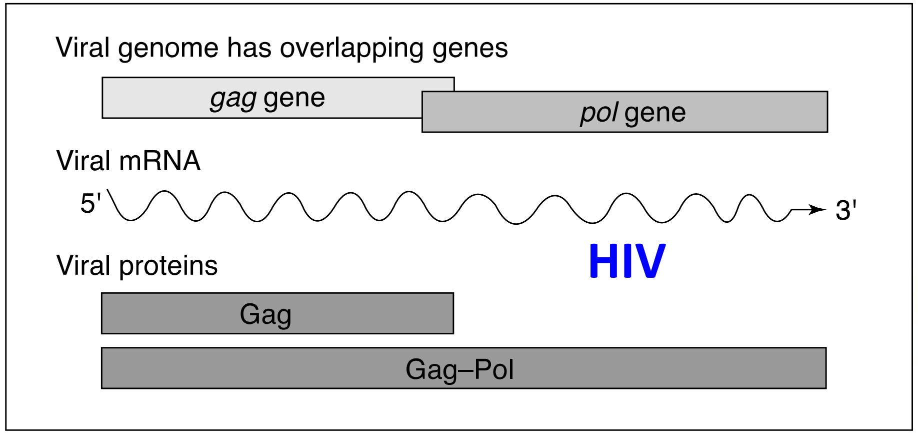
Accuracy

For polymerase motors, **accuracy** is as important, if not more, as the **speed.**



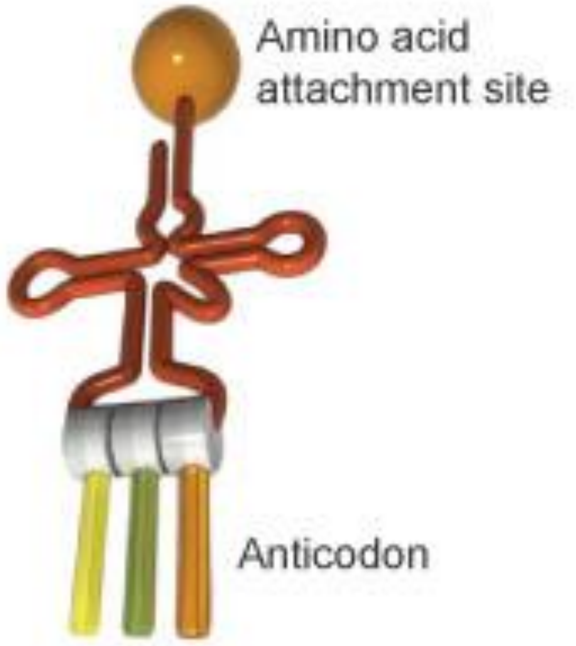
# "*Programmed*" Errors: Unconventional Translation



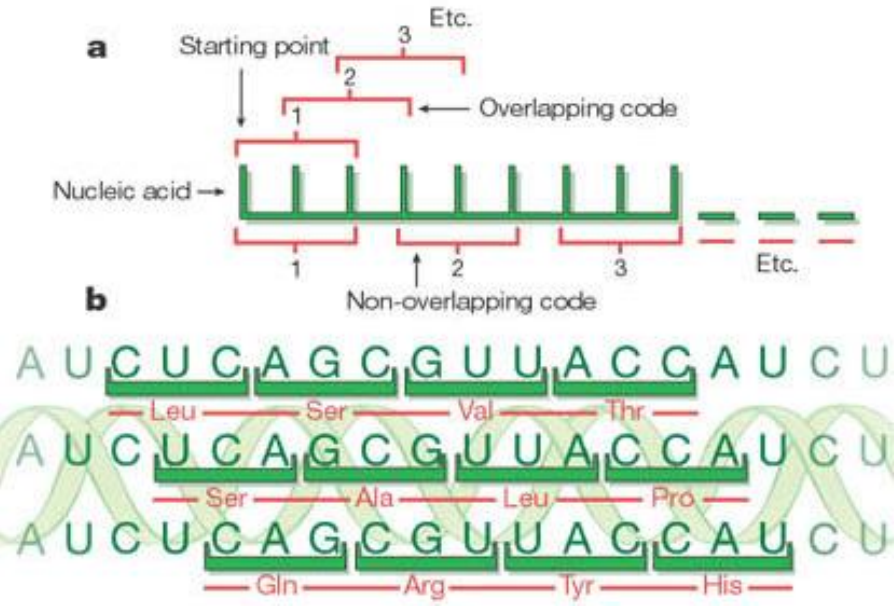



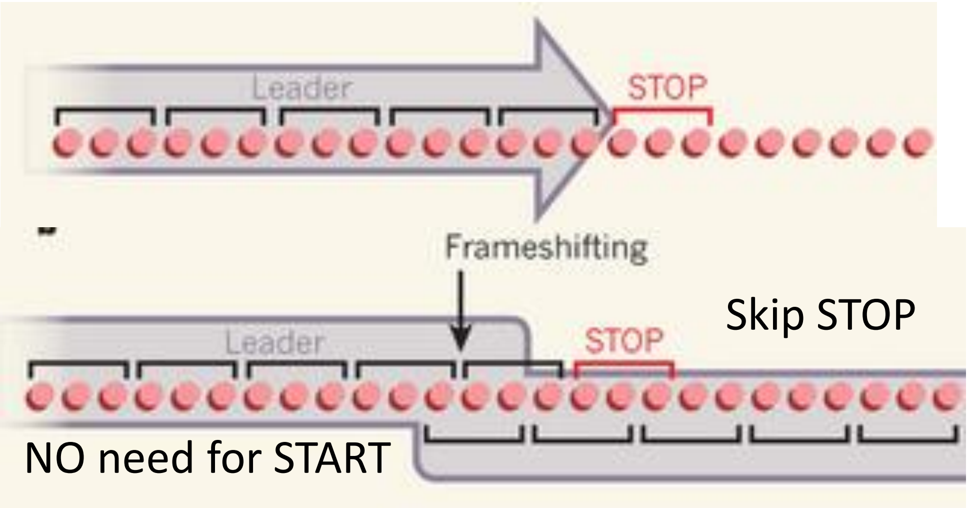

Dinman et al.
TIBSTECH (1998)

From: Nature Education



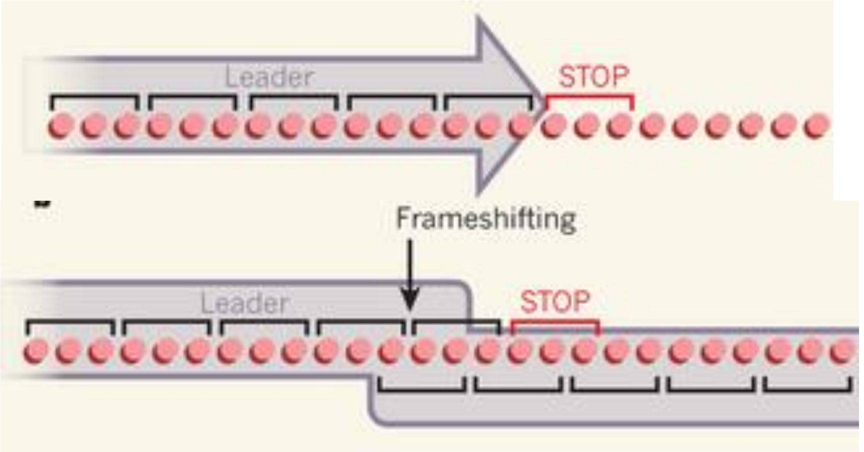

Atkins & Gesteland, Nature 414, 693 (2001)



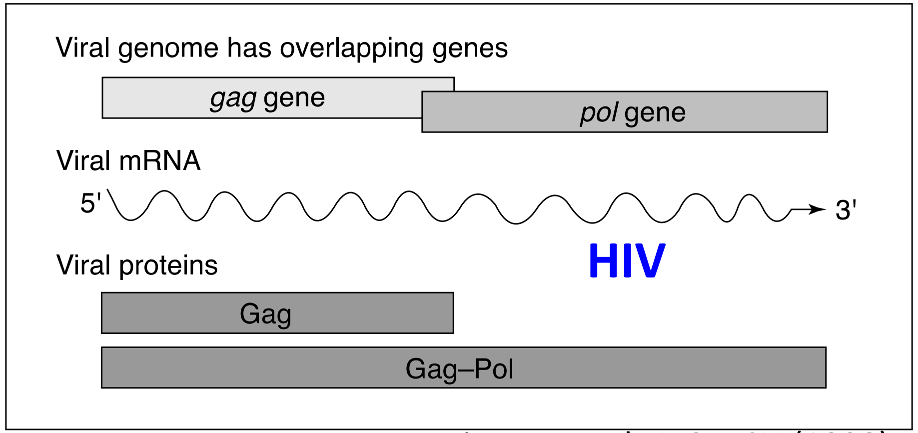




Atkins & Baranov, Nature 503, 478 (2013)

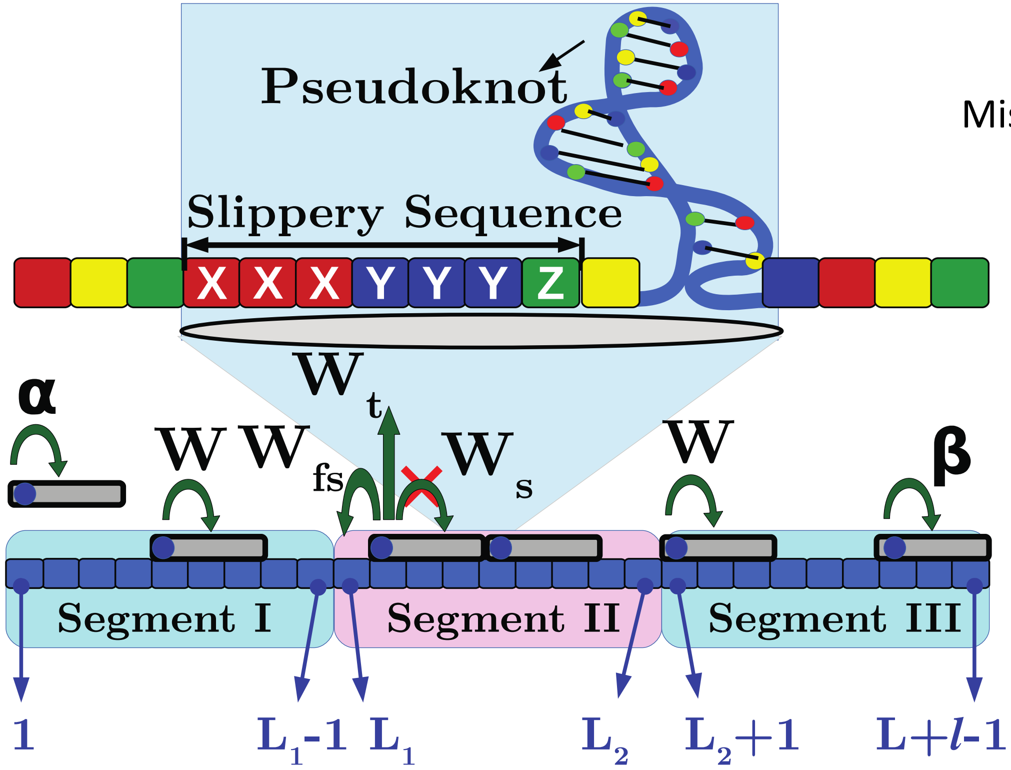
# Non-canonical Elongation: Frameshifting



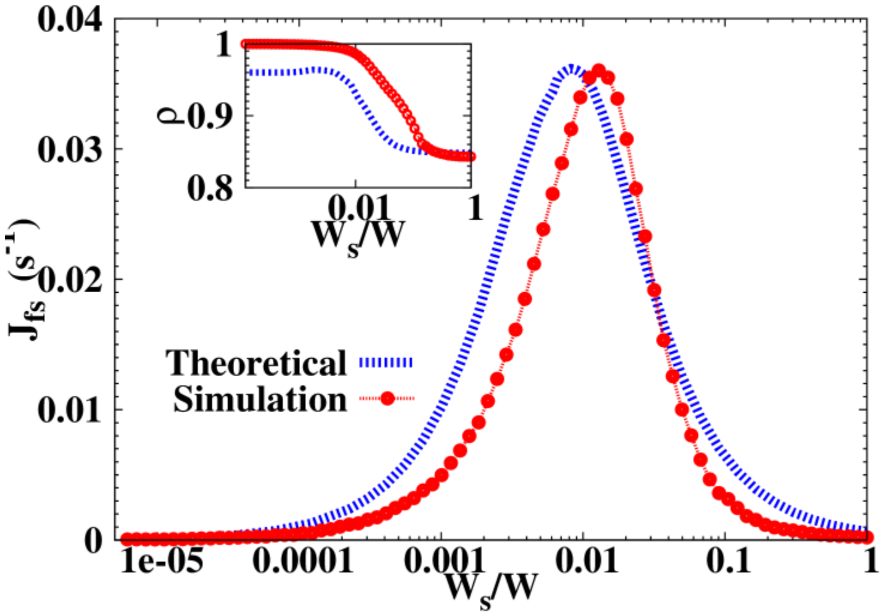

Atkins & Baranov, Nature 503, 478 (2013)




Dinman et al.TIBSTECH (1998)




Mishra, Schutz & Chowdhury EPL 114, 68005 (2016)



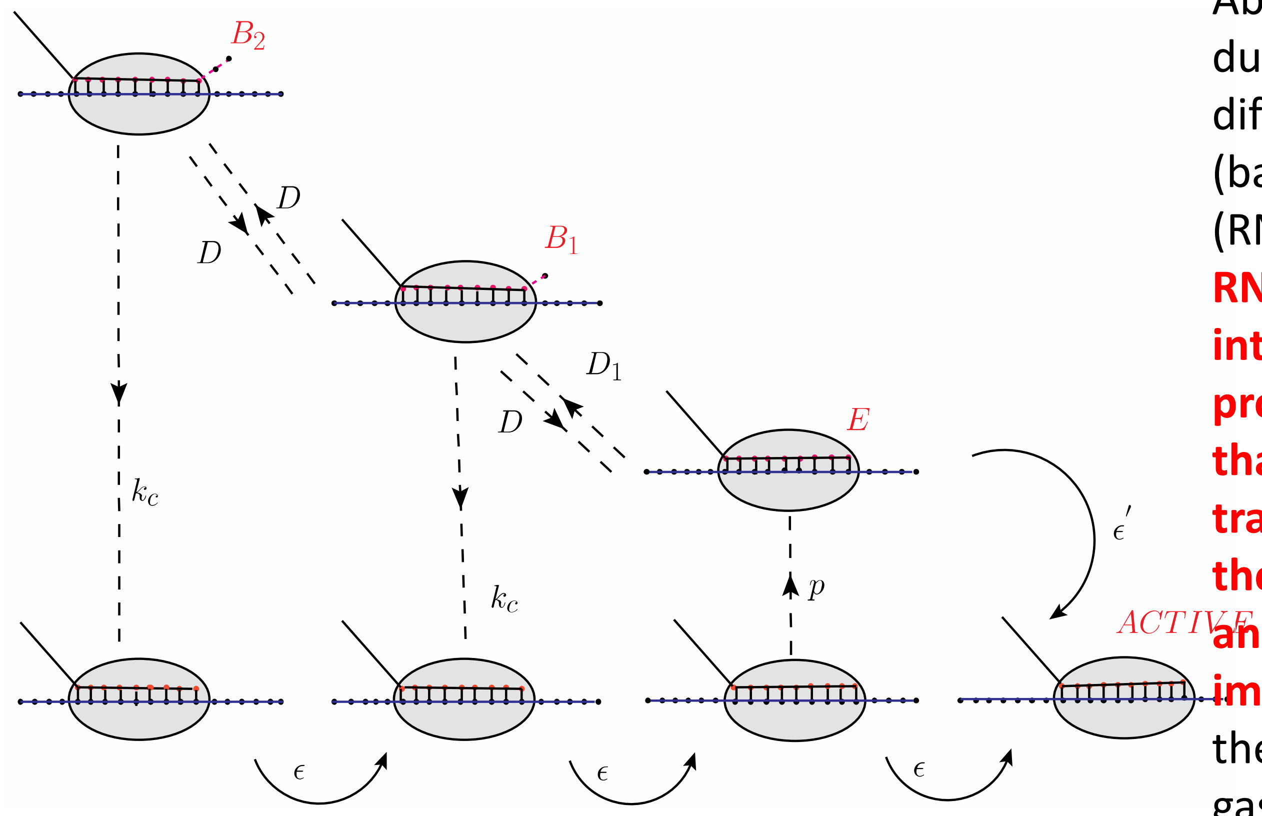
A Letters Journal Exploring the Frontiers of Physics

EPL, **96** (2011) 60004
doi: 10.1209/0295-5075/96/60004

# Transcriptional proofreading in dense RNA polymerase traffic

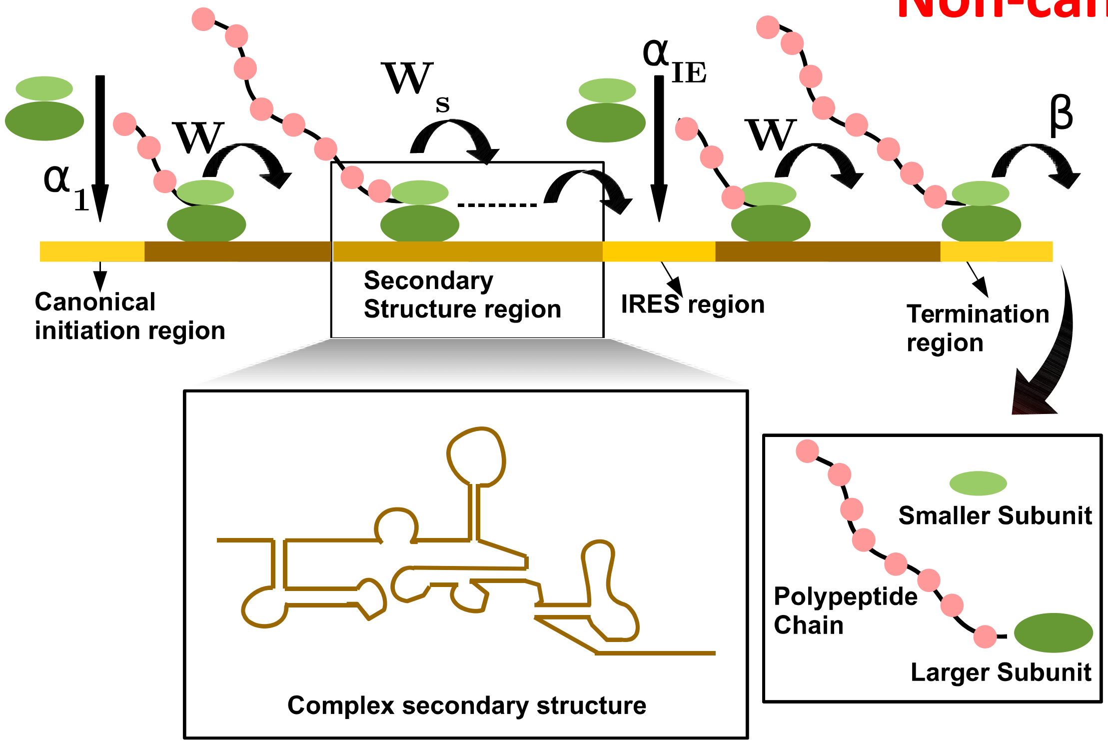
Mamata Sahoo and Stefan Klumpp[(a)]

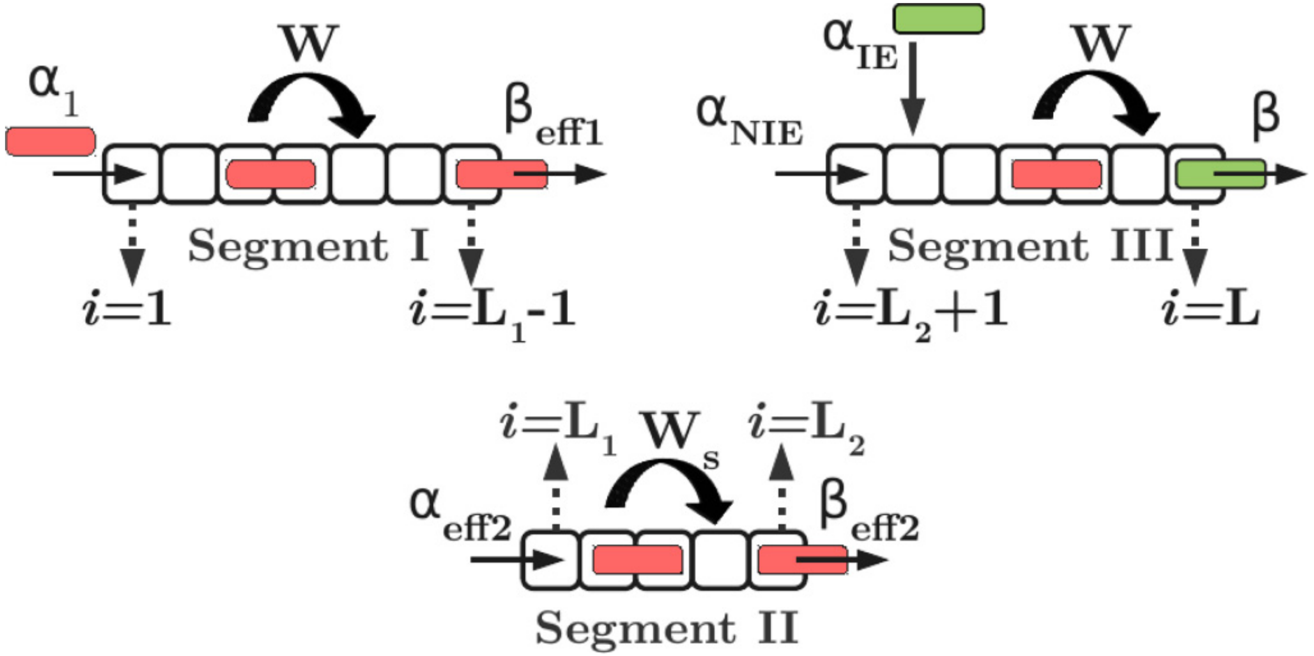
*Max Planck Institute of Colloids and Interfaces, Science Park Golm - 14424 Potsdam, Germany, EU*




Abstract – The correction of errors during transcription involves the diffusive backward translocation (backtracking) of RNA polymerases (RNAPs) on the DNA. **A trailing RNAP on the same template can interfere with backtracking as it progressively restricts the space that is available for backward translocation and thereby ratchets the backtracked RNAP forward. We analyze the resulting negative impact on proofreading** theoretically using a driven lattice gas model of transcription under conditions of dense RNAP traffic.

# Non-canonical Initiation: IRES




Mishra and Chowdhury, Phys. Rev. E (2017)

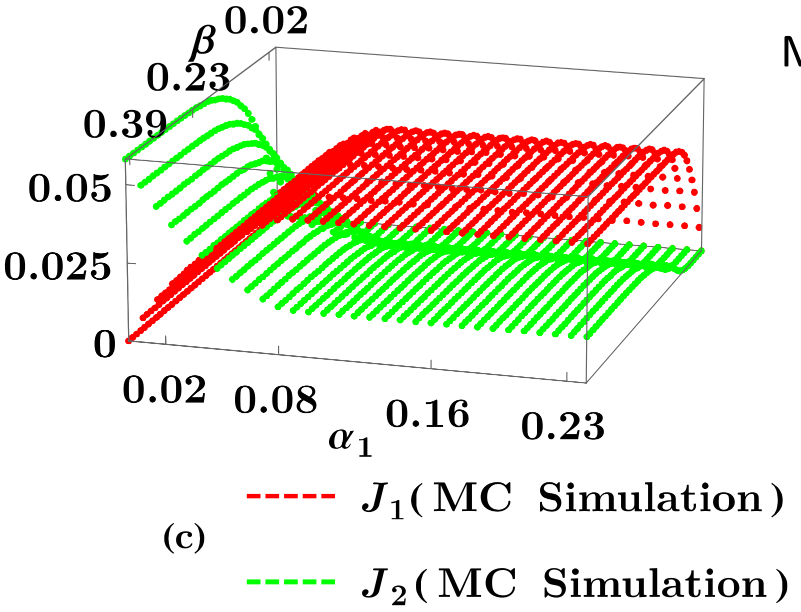
TABLE II. The effective rate constants and their defining expressions.

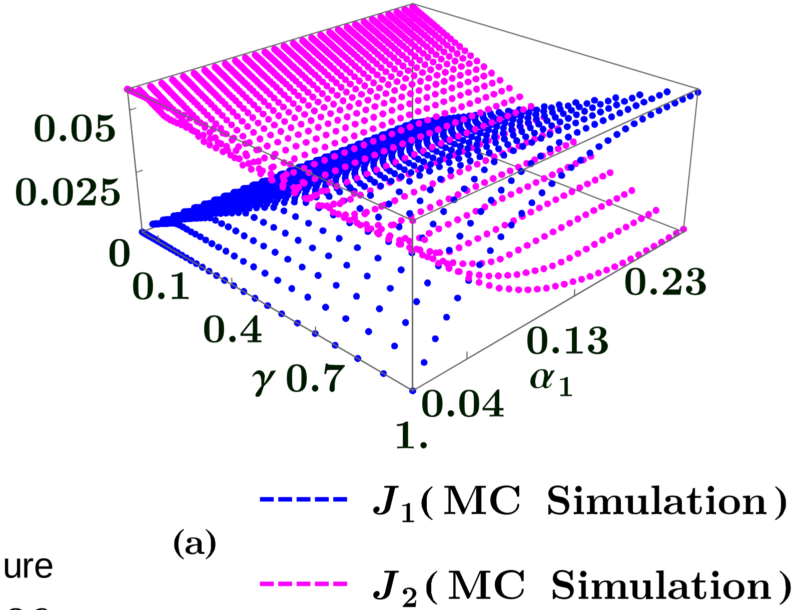
| Rate constant | Expression |
|---|---|
| $\alpha_{\text{eff2}}$ | $\alpha_{\text{eff2}} = W\rho_{c1}/\ell$ |
| $\alpha_{\text{NIE}}$ | $\alpha_{\text{NIE}} = W_s\rho_{c2}/\ell$ |
| $\alpha_{\text{eff3}}$ | $\alpha_{\text{eff3}} = \alpha_{\text{NIE}} + \alpha_{\text{IE}}$ |
| $\beta_{\text{eff1}}$ | $\beta_{\text{eff1}} = W P_1(\underline{L_1 - 1}\mid L_1 + \ell - 1)$ |
| $\beta_{\text{eff2}}$ | $\beta_{\text{eff2}} = W_s P_1(\underline{L_2}\mid L_2 + \ell)$ |

**Internal Ribosome Entry Site (IRES): An Unconventional mode of Translation**

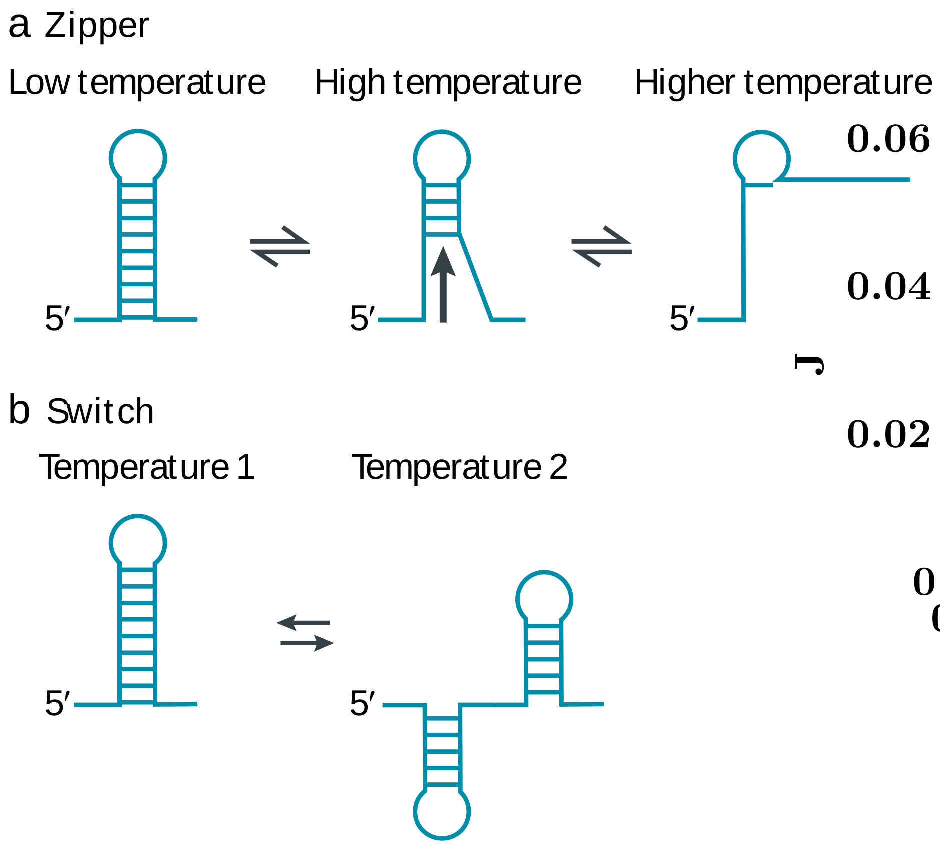
Mishra and Chowdhury, Phys. Rev. E (2017)

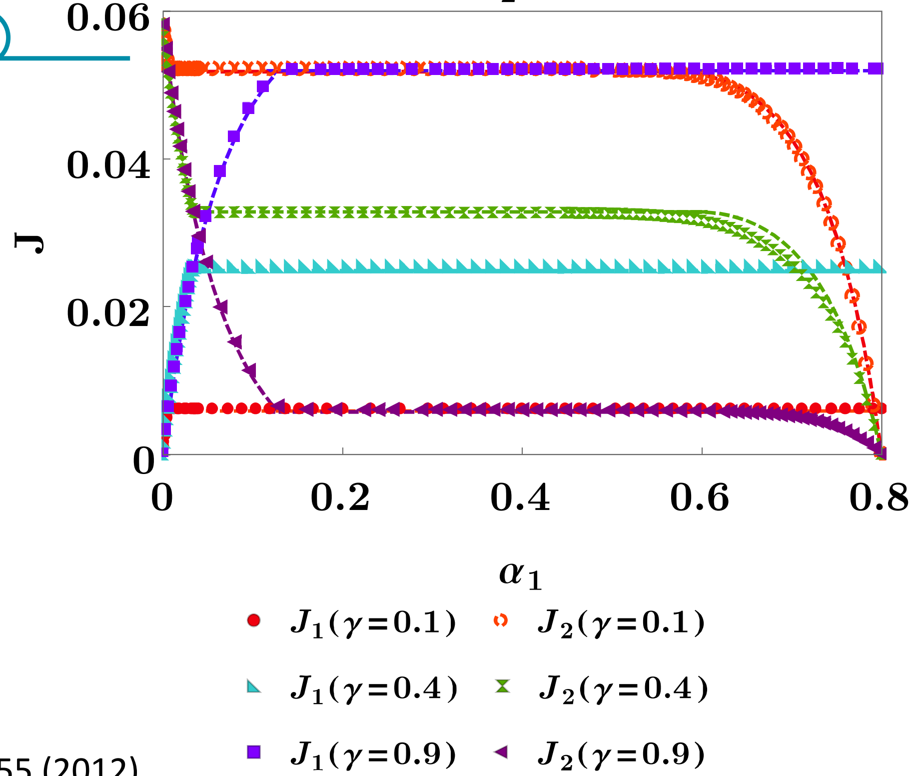
**Translational Interference?**




## Bacterial RNA thermometers




Kortmann and Narberhaus, Nat. Rev. Microbiol. 10, 255 (2012)

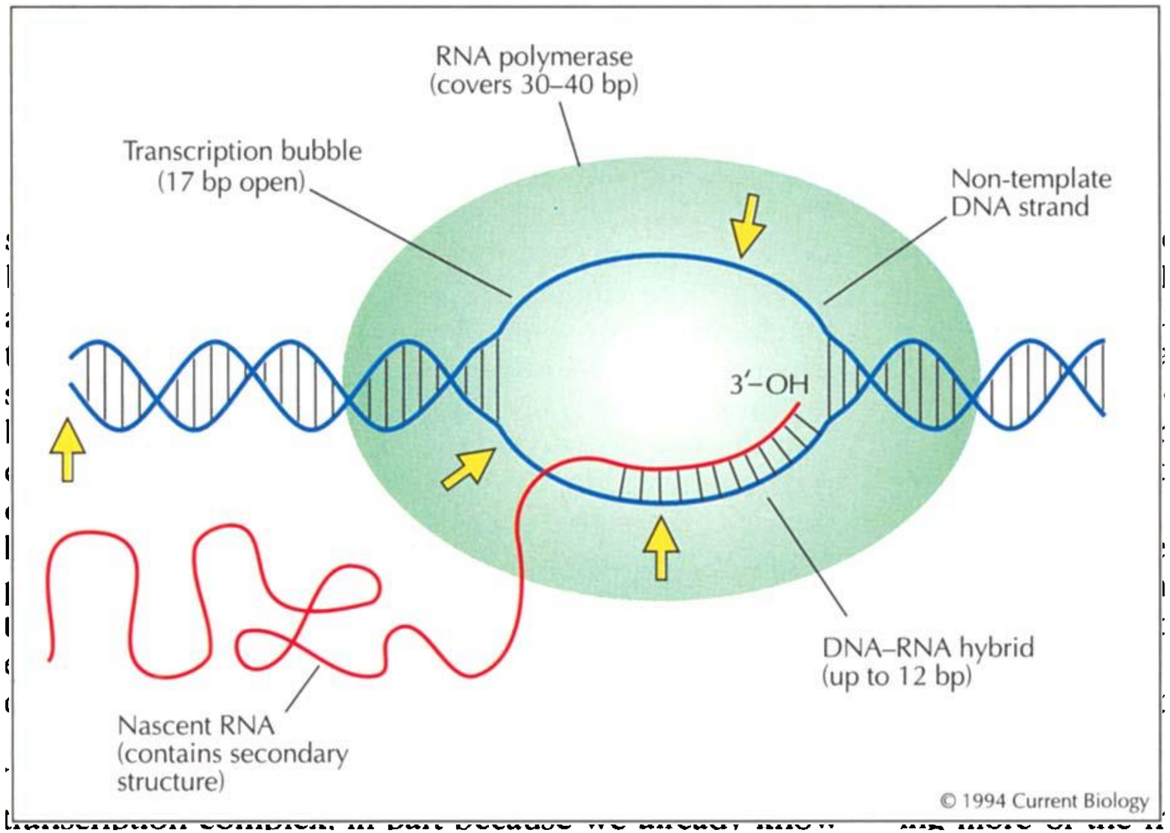
Spatio-temporal organization of RNAP motors on DNA track

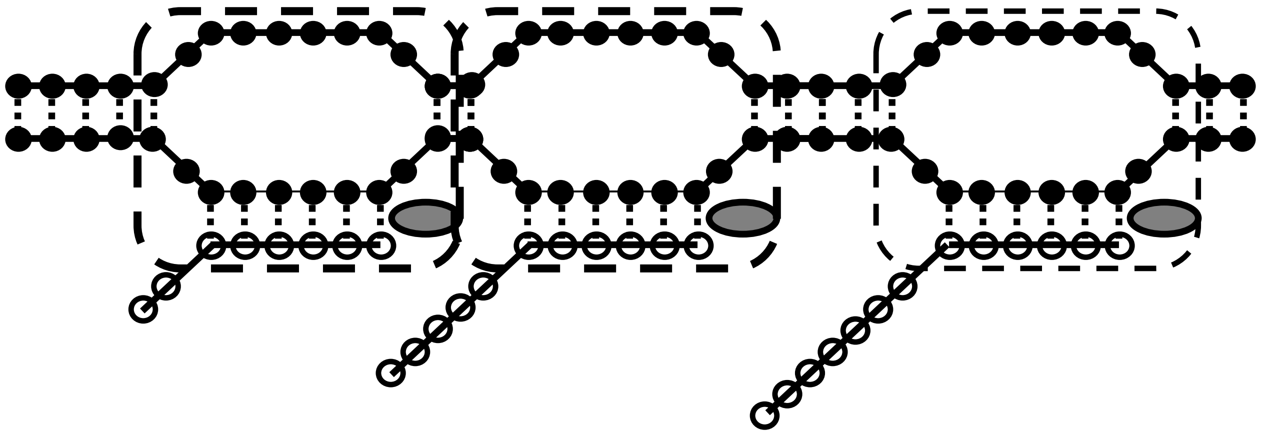
during Transcription:

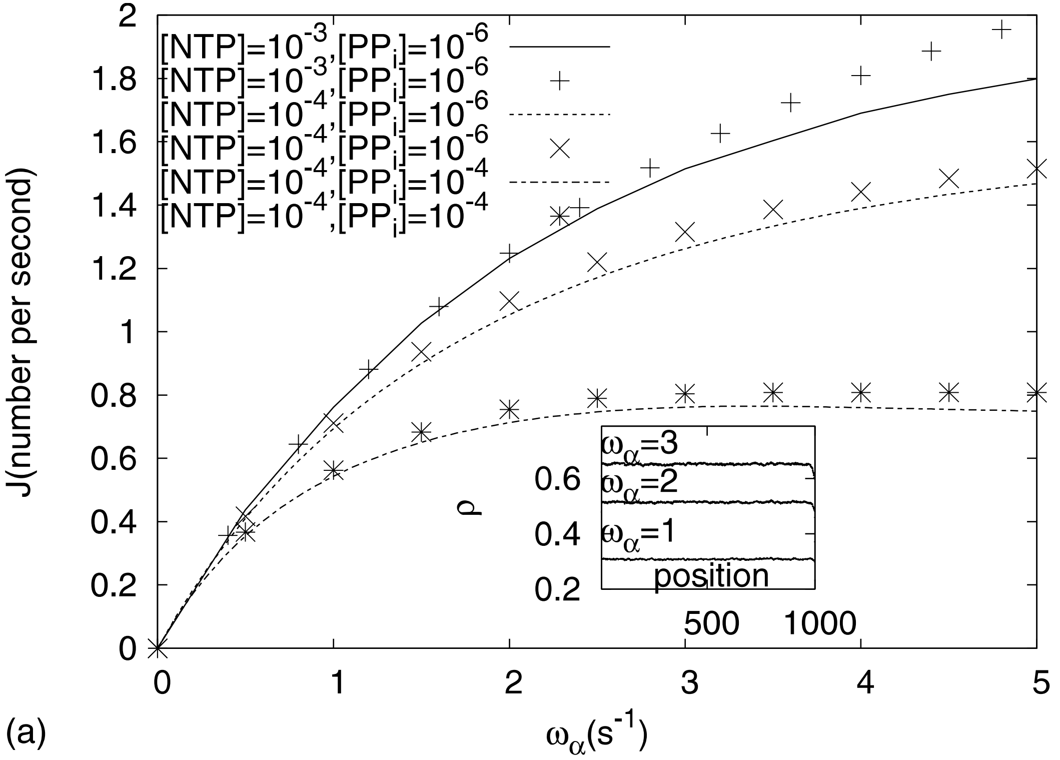
effects of mechano-chemical cycles of individual RNAPs

# Theoretical model of RNAP and RNA synthesis

T. Tripathi and D. Chowdhury, Phys. Rev. E 77, 011921 (2008)






(a)

Transcription-elongation complex (TEC)

= RNAP + DNA template

+ mRNA transcript

Mechano-chemistry of each RNAP
+ Steric interactions

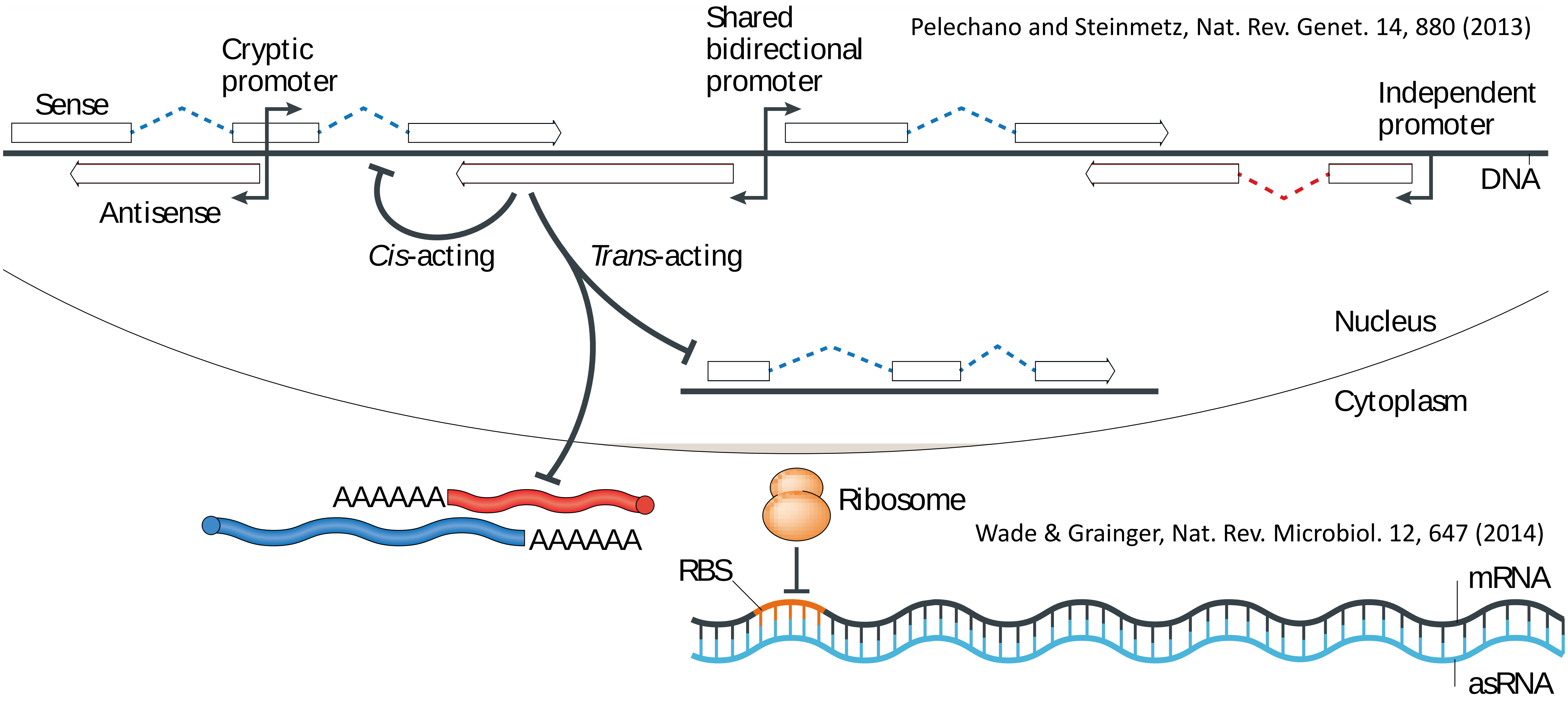
Regulation of RNAP Traffic on DNA template strand

with overlapping genes:

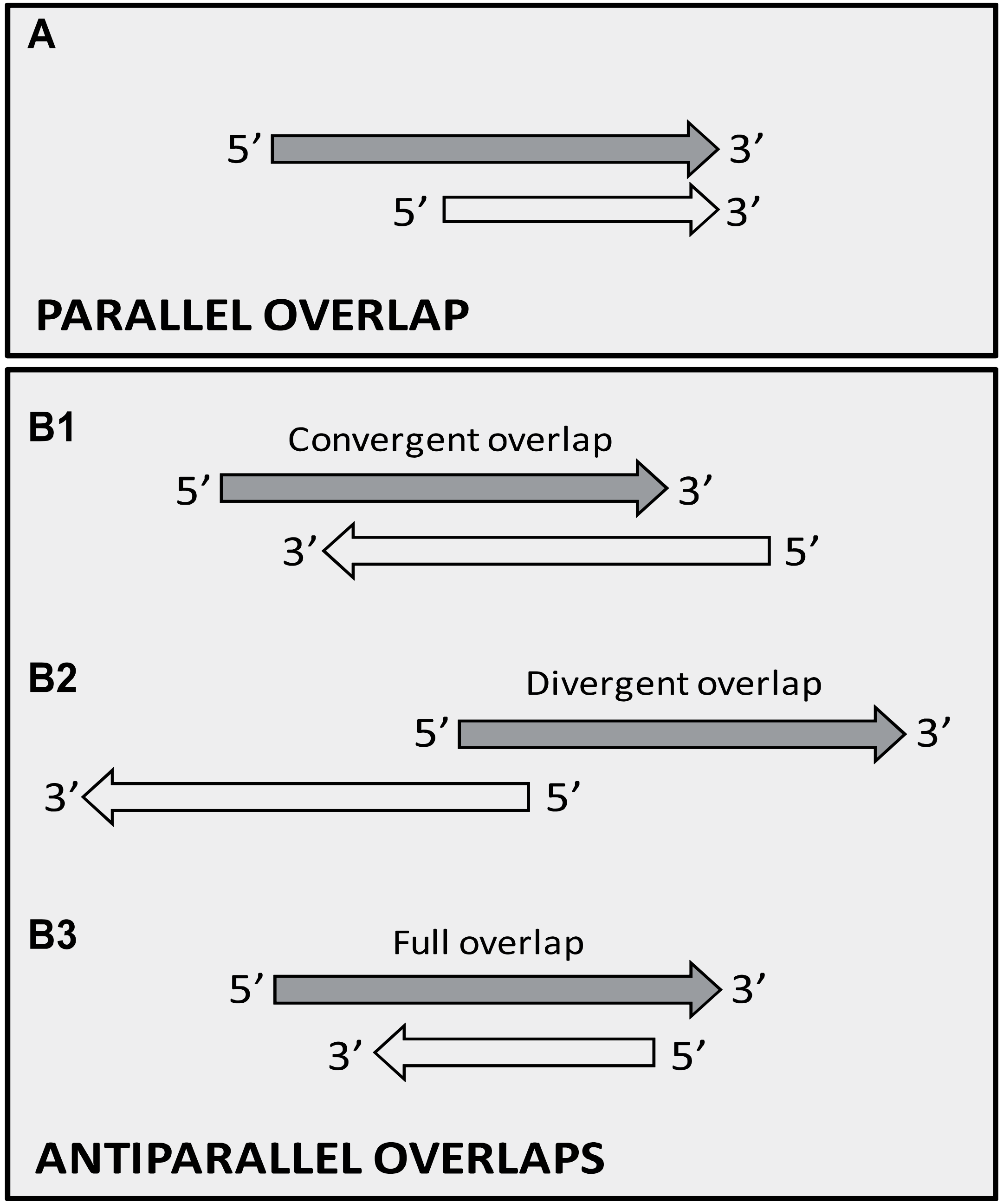
Consequences of Transcriptional Interference

- Antisense transcripts are transcribed from the strand opposite to that of the sense transcript.
- Like transcription factors, these are also regulators of gene expression.
- These can establish on-off (bi-stable) switches.

## Classification of Anti-Sense Transcripts

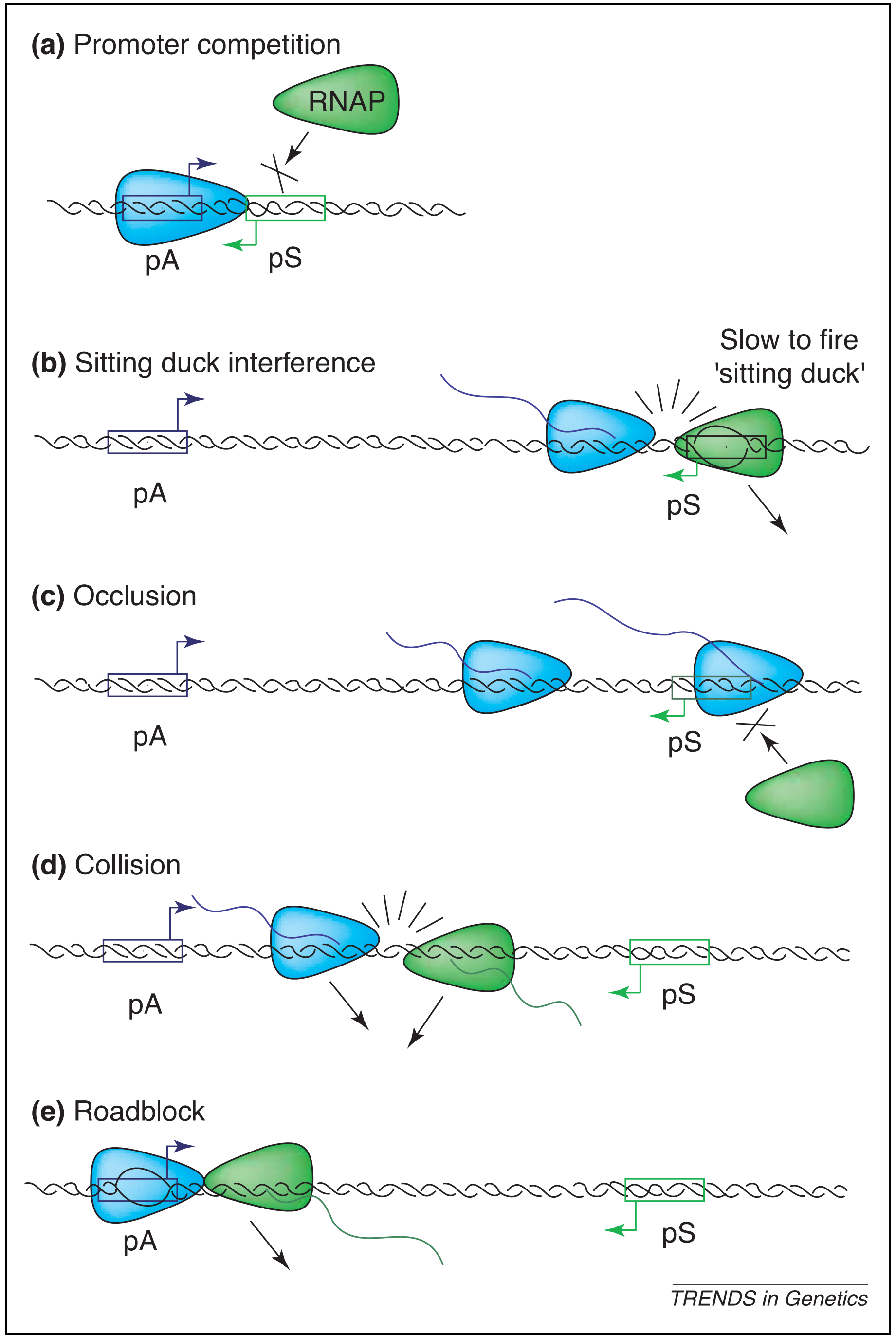


Overlapping/Nested Genes




Z. Boldogkoi, Front. Genet. (2012)

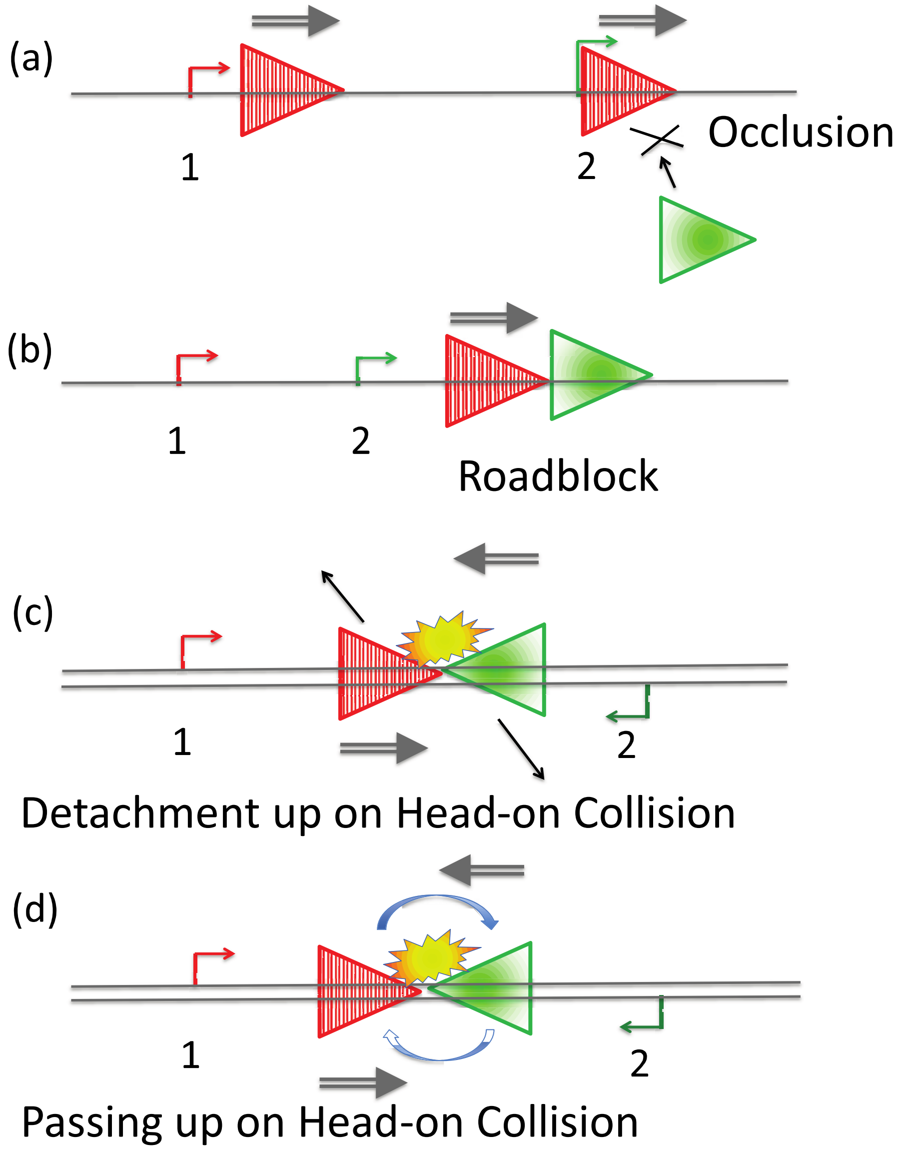
**Co-Transcriptional effects of antisense transcription: Transcriptional Interference**

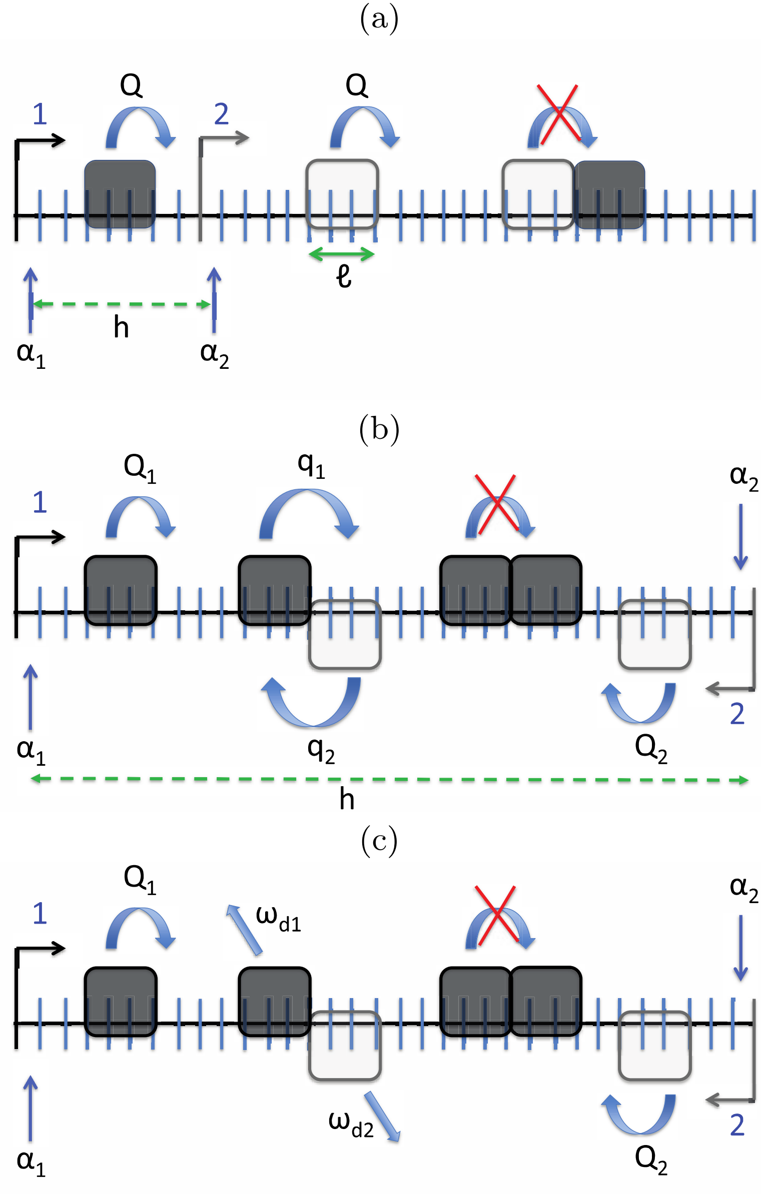



Shearwin et al. Trends in Genet. (2005)

# Transcriptional Interference

Ghosh, Bameta, Ghanti, Chowdhury, J. Stat. Mech.: Theor. & Expt. (2016)



Co-directional TI

$$\frac{\mathrm{d}P_1(1,t)}{\mathrm{d}t} = \underbrace{\alpha_1\left(1-\sum_{s=1}^{\ell} P(s)\right)}_{\text{Entry at ON}-\text{ramp}} - \underbrace{QP_1(1,t)\,\xi(\underline{1}|1+\ell)}_{\text{Forward Hopping from } j=1},$$

$$\frac{\mathrm{d}P_1(i,t)}{\mathrm{d}t} = \underbrace{QP_1(i-1,t)\xi(\underline{i-1}|i-1+\ell)}_{\text{Forward Hopping to } j=i} - \underbrace{QP_1(i,t)\xi(\underline{i}|i+\ell)}_{\text{Forward Hopping from } j=i} \quad \text{for, } (1<i<L_1),$$

$$\frac{\mathrm{d}P_1(L_1,t)}{\mathrm{d}t} = \underbrace{QP_1(L_1-1,t)\xi(\underline{L_1-1}|L_1-1+\ell)}_{\text{Forward Hopping to } j=L_1} - \underbrace{\beta P_1(L_1,t)}_{\text{Exit at OFF}-\text{ramp}}.$$

$$\frac{\mathrm{d}P_2(1+h,t)}{\mathrm{d}t} = \alpha_2\xi(1+h)\left(1-\sum_{s=1}^{\ell} P(s+h)\right) - QP_2(1+h,t)\,\xi(\underline{1+h}|1+h+\ell),$$

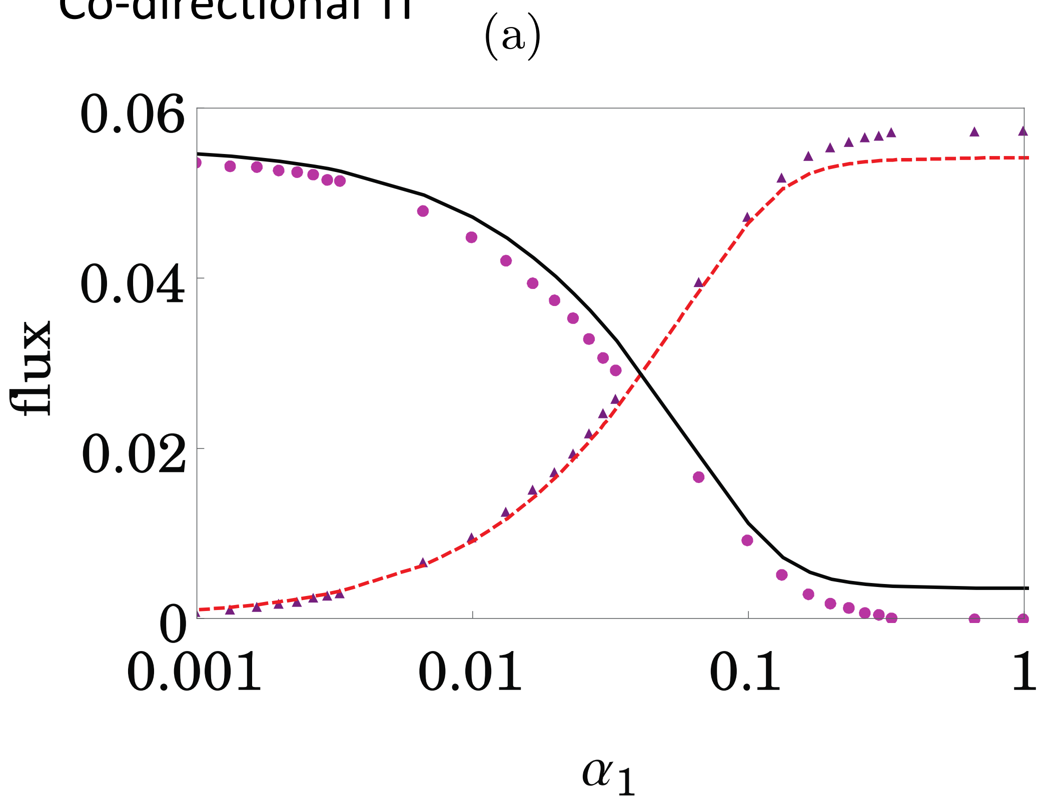
$$\frac{\mathrm{d}P_2(i,t)}{\mathrm{d}t} = QP_2(i-1,t)\xi(\underline{i-1}|i-1+\ell) - QP_2(i,t)\xi(\underline{i}|i+\ell)$$

$$\text{for , } (1+h<i<L_2+h),$$

$$\frac{\mathrm{d}P_2(L_2+h,t)}{\mathrm{d}t} = QP_2(L_2+h-1,t)\xi(\underline{L_2+h-1}|L_2+h-1+\ell) - \beta P_2(L_2+h,t).$$

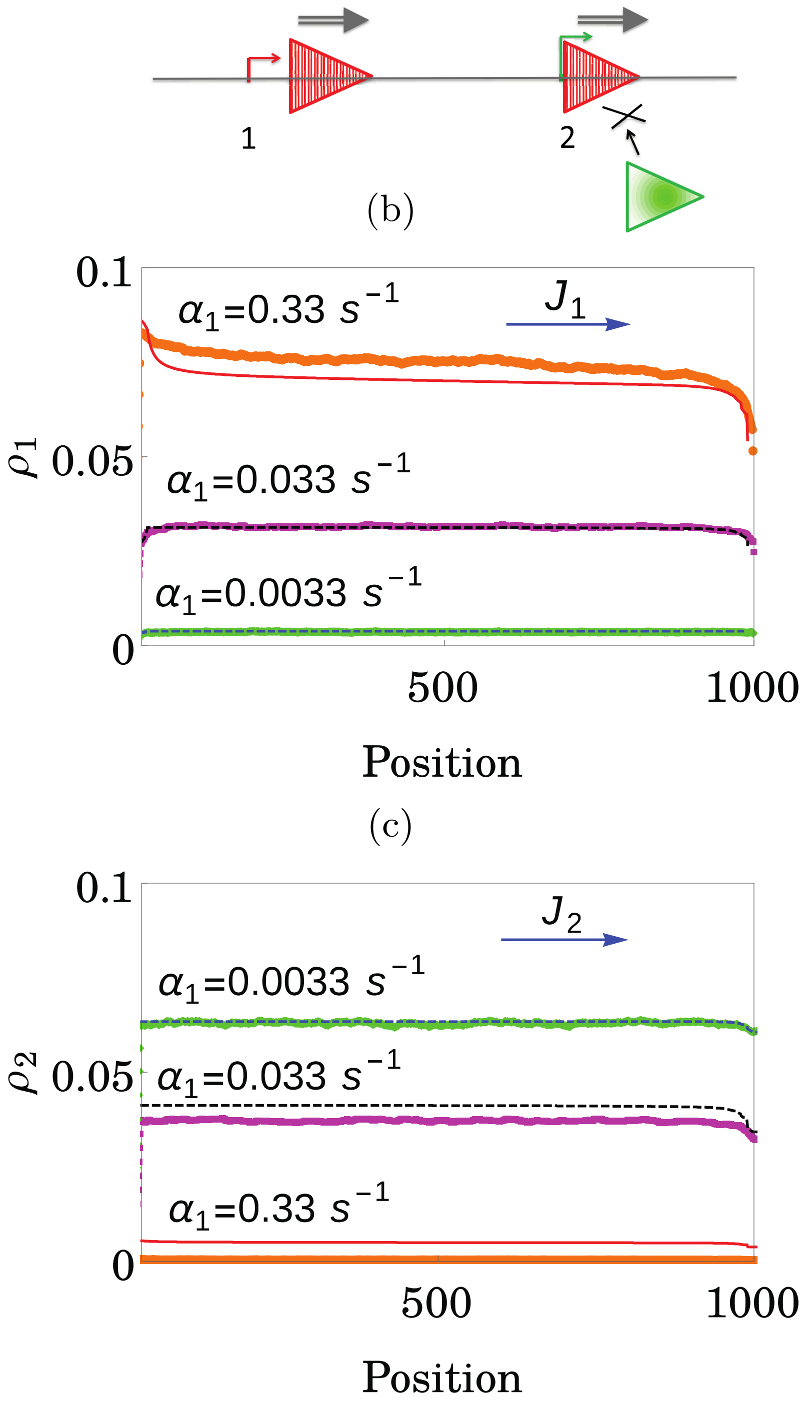
$$\xi(\underline{i}|i+\ell) = \frac{1-\sum_{s=1}^{\ell} P(i+s)}{1+P(i+\ell)-\sum_{s=1}^{\ell} P(i+s)}.$$

Co-directional TI

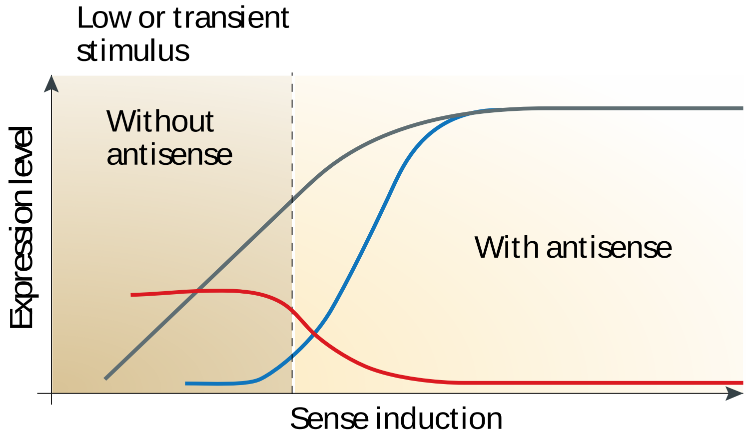



**The pair can form a bistable switch: it can be in either 'ON' state (first gene is expressed and second gene is repressed) or in an 'OFF ' state (first gene is repressed and the second gene is expressed)**

**.**




Pelechano and Steinmetz, Nat. Rev. Genet. 14, 880 (2013).




Ghosh et al. J. Stat Mech. Theor. Expt (2016)

**Contra**-directional TI **with Passing without detachment**. (Phage RNAPs)

In a Head-on Collision, Two RNA Polymerases Approaching One Another on the Same DNA May Pass by One Another

Na Ma[1,2,3] and William T. McAllister[1,4]

J. Mol. Biol. (2009) 391, 808–812

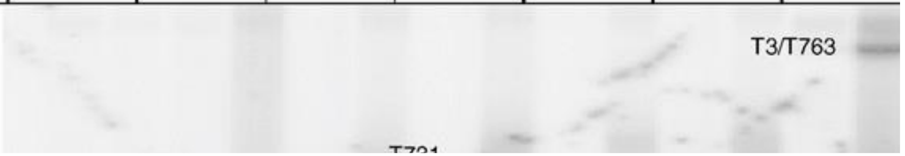
***"To allow two polymerases to move toward one another in a controlled manner, a template was constructed that contains a promoter for T7 RNAP and a promoter for T3 RNAP arranged in opposite directions."***

(f)

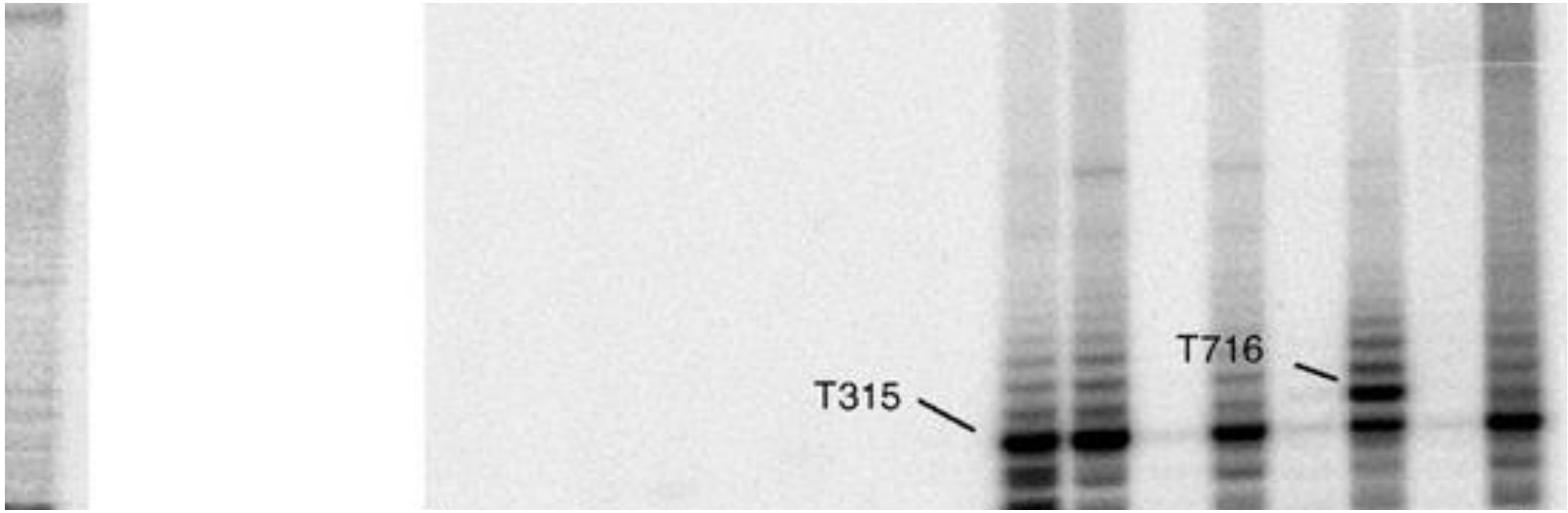
| Step | NTP | T3 EC | H-T7 EC | Dis |
|---|---|---|---|---|
| 1 | G,A* | - | 15* | NA |
| Immobilize | | - | 15* | NA |
| 2 | G,A* | 13* | 15* | 16 |

(g)

| Step | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|

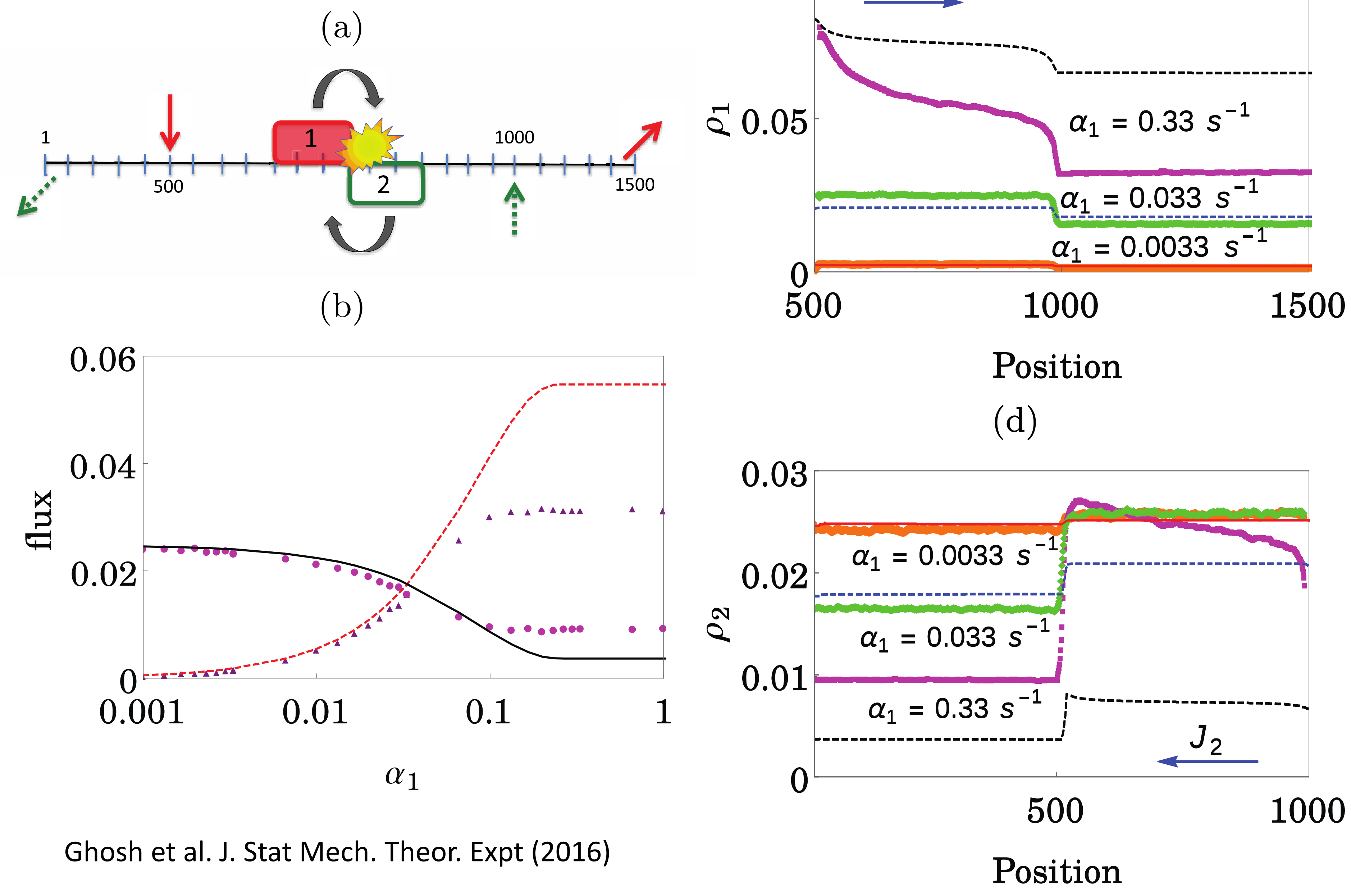



***T7 could advance past halted T3 EC and after collision halted T3 EC could resume transcription***.




***Since RNAPs moving in opposite directions use two different strands of the DNA as their templates, it seems likely that they manage to pass by one other by temporarily releasing their non-template strand while maintaining association with their template strand.***

Contra-directional TI with Passing without detachment




Ghosh et al. J. Stat Mech. Theor. Expt (2016)

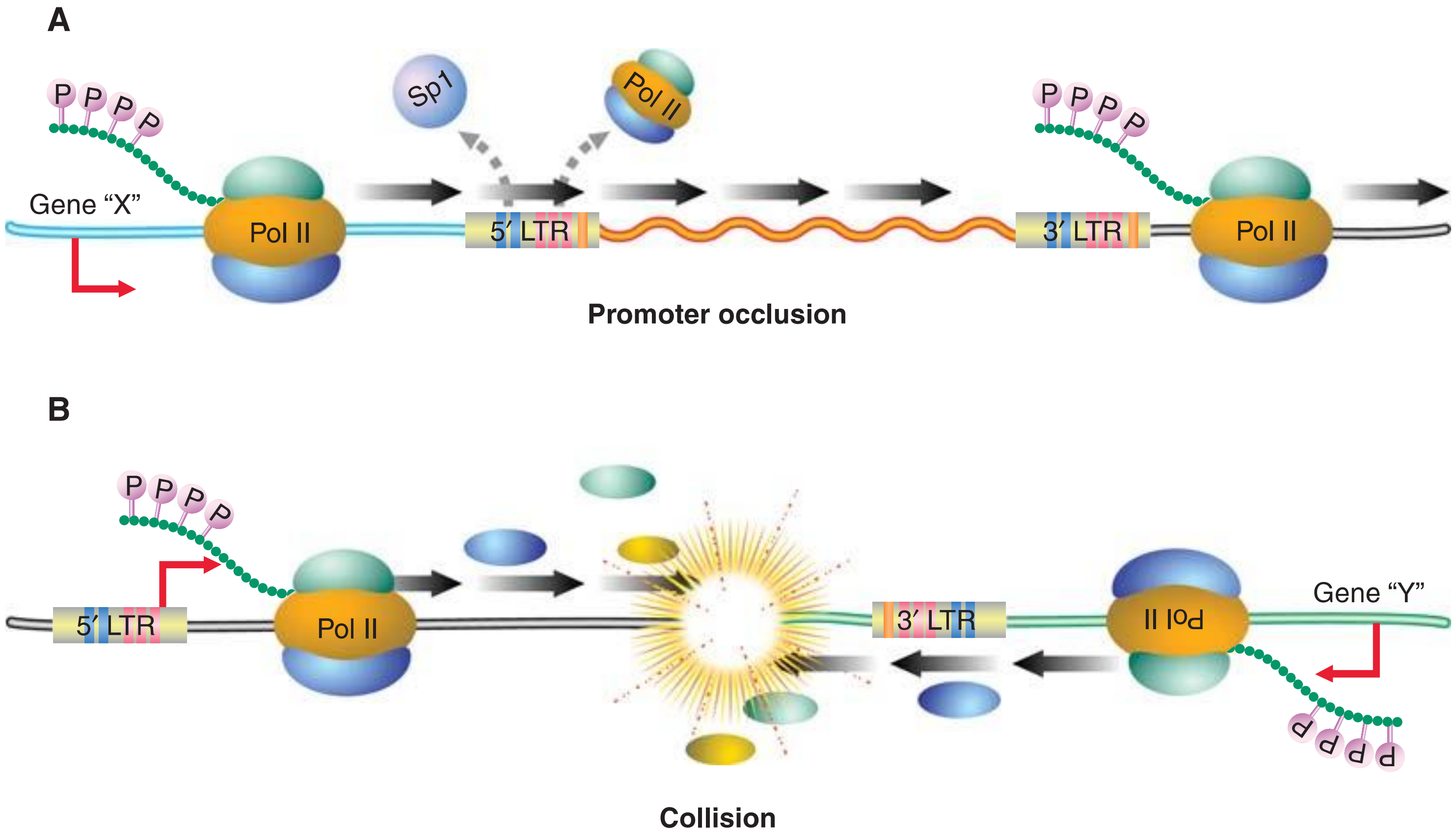
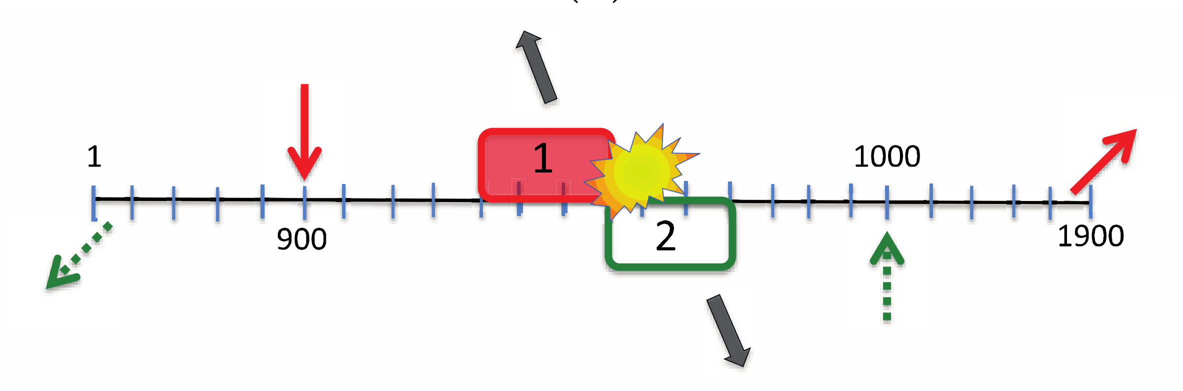



**Figure 3.** Two scenarios in which transcriptional interference may promote HIV-1 latency. In the first case, the HIV-1 provirus is integrated in the same polarity as an upstream gene within an intron of this gene. Read through by RNA Pol II initiating at the upstream promoter occludes the 5′LTR and displaces key transcription factors thereby promoting viral latency. Alternatively, the HIV-1 provirus and the cellular gene may be arranged in opposite polarity. In this situation, initiating polymerases collide, leading to decreased expression of one or both transcription units. The fact that latent HIV-1 proviruses are commonly found in actively transcribed genes suggests that transcriptional interference may be important in the maintenance of proviral latency.

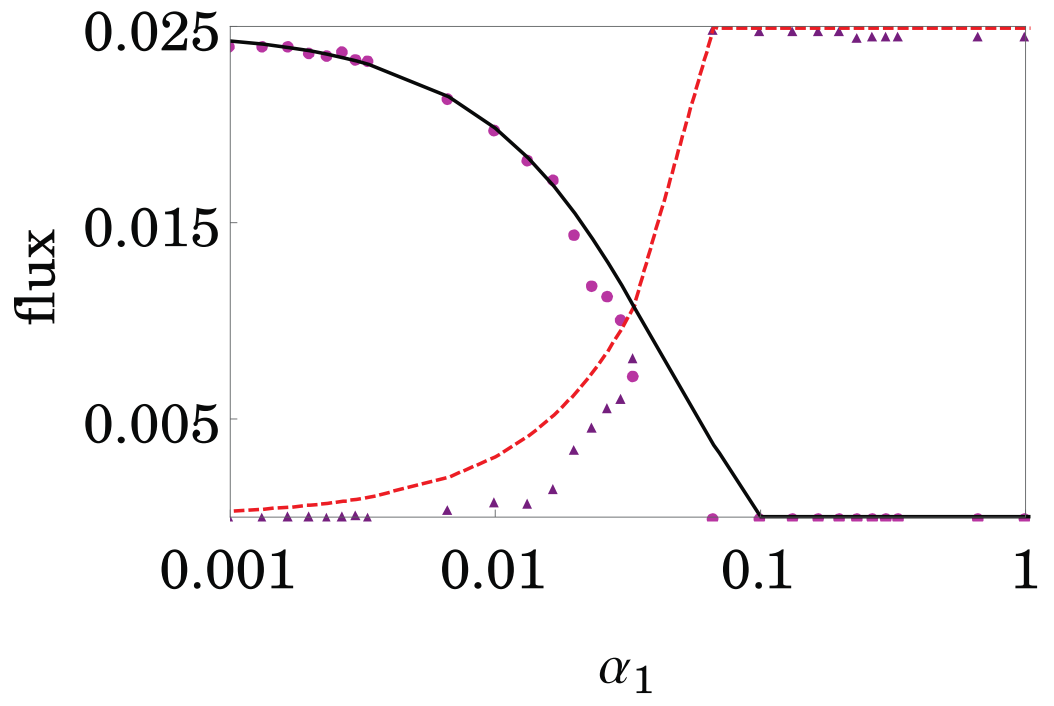
 doi: 10.1101/cshperspect.a007096
Cite this article as *Cold Spring Harb Perspect Med* 2011;1:a007096

Contra-directional TI with Detachment without Passing

(a)




(b)

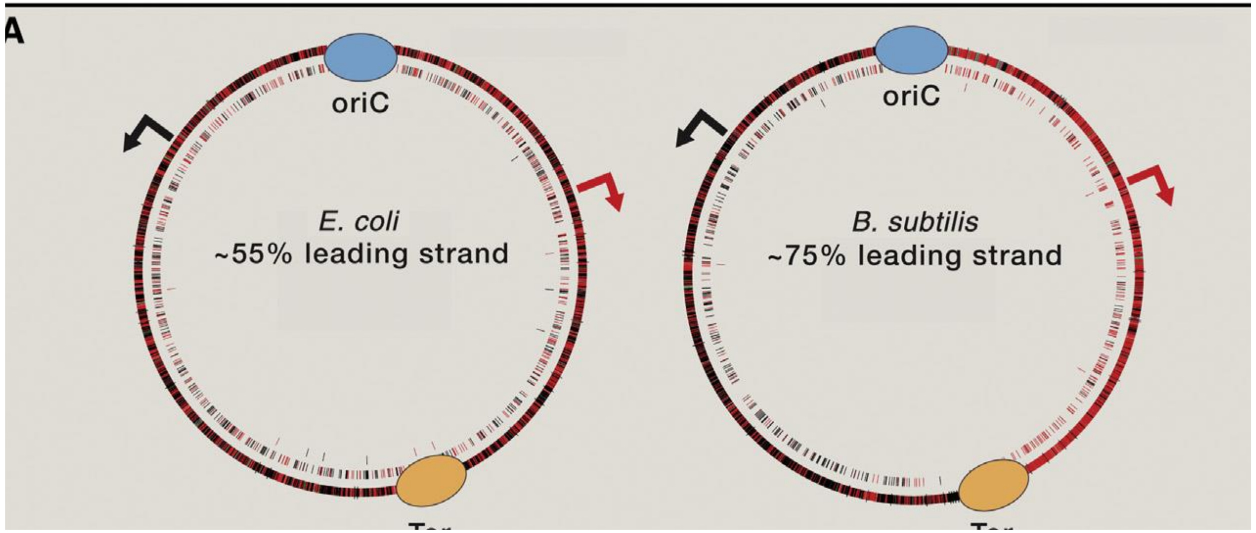


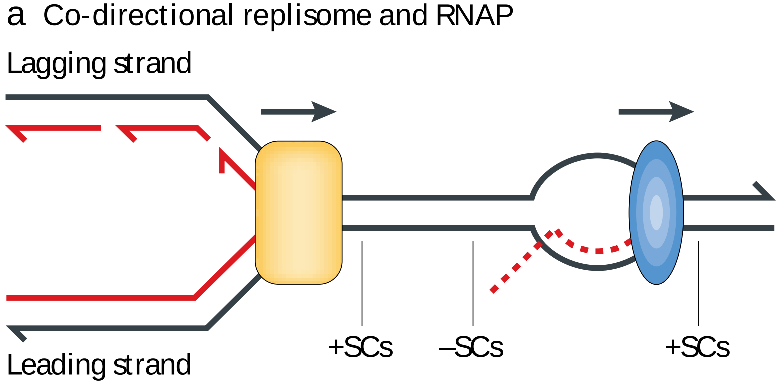

Ghosh et al. J. Stat Mech. Theor. Expt (2016)

# Collision of RNAP motors and Replisome on DNA track during simultaneous Transcription and Replication: resolution of transcription-replication conflict

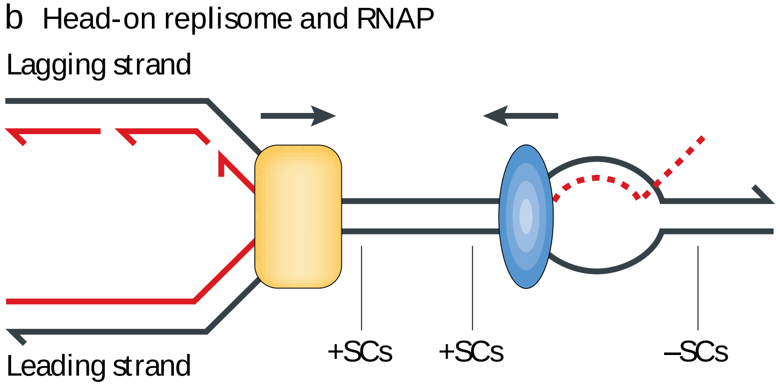
# Genome wide Transcription and Replication: Conflict Resolution

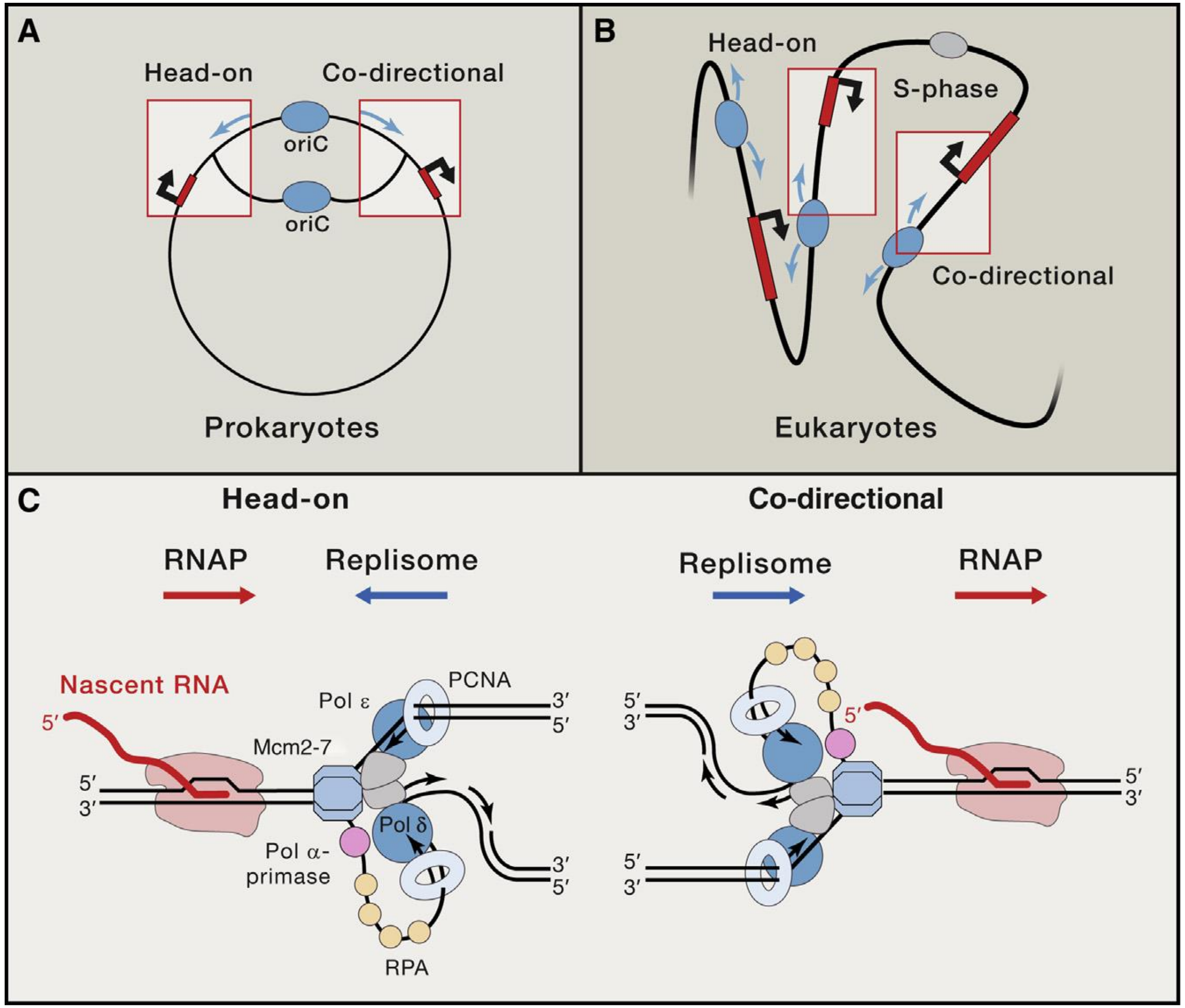
Hamperl and Cimprich, Cell 167, 1455 (2016)




Kim and Robertson, Nat. Rev. Genrt. 13, 204 (2012)



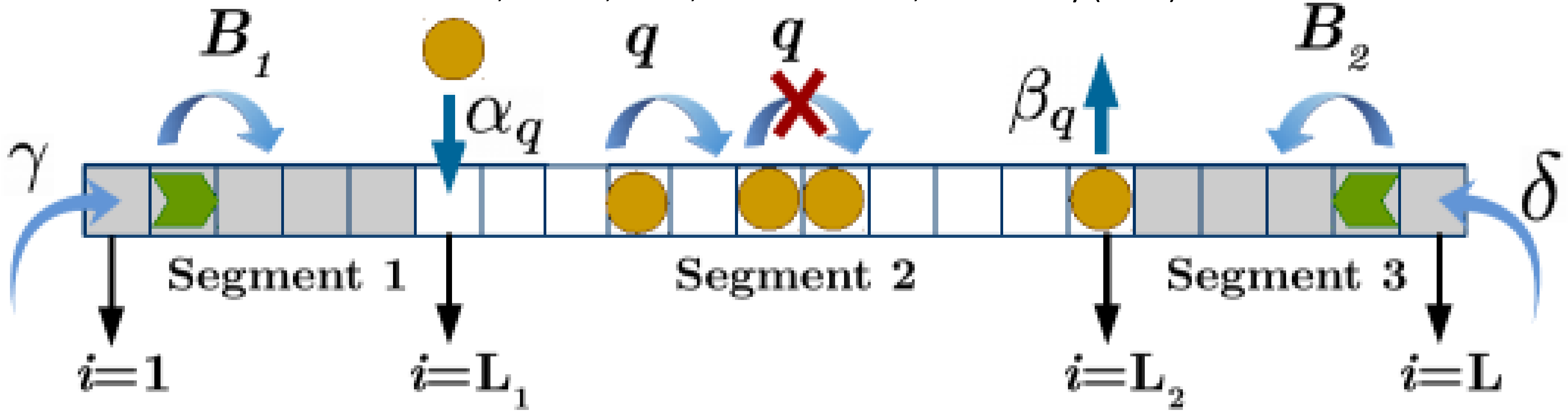



Codirectional encounters

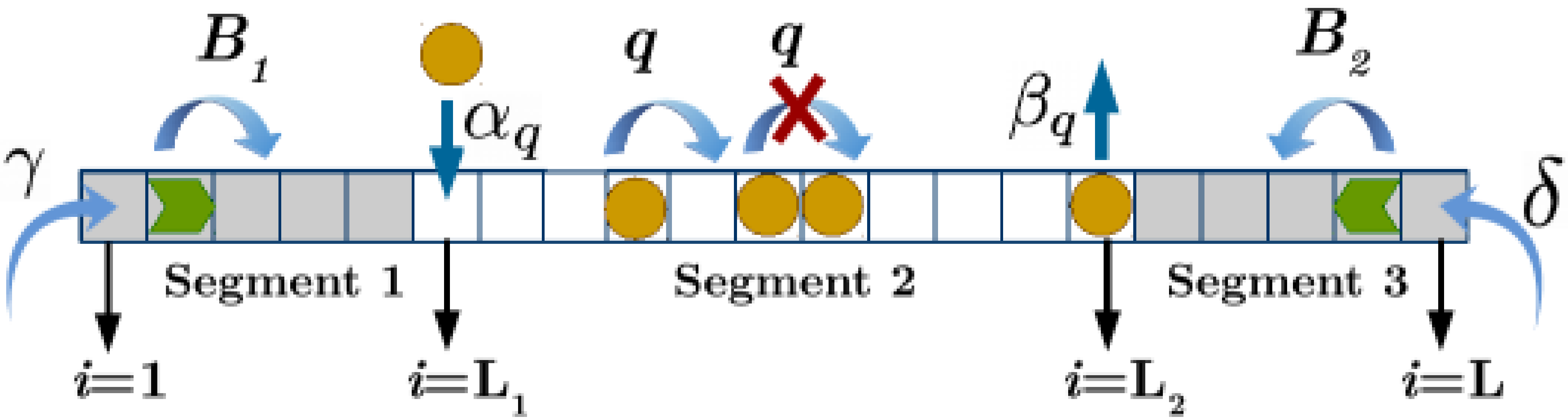
Helmrich, Ballarino, Nudler, Tora, Nat. Struct. Mol. Biol.20, 412 (2013)

Head-on encounters

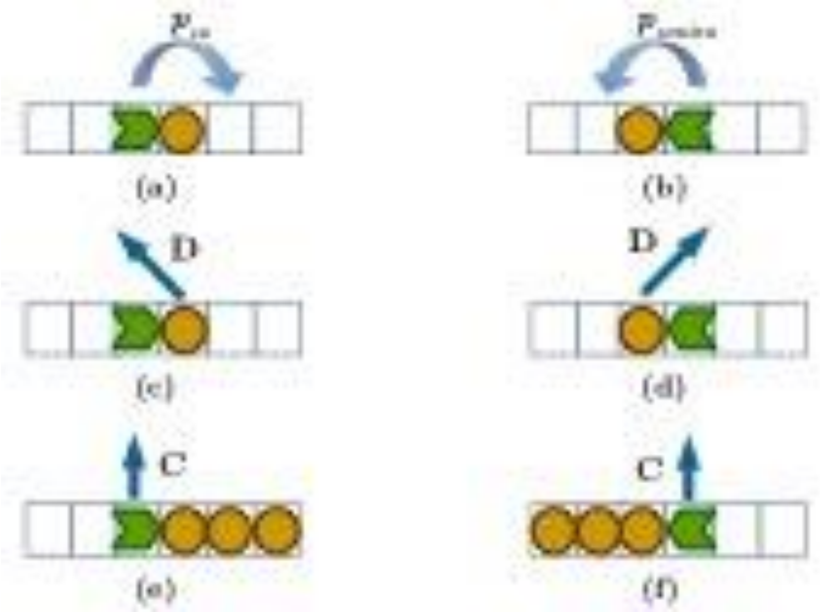

Ghosh, Mishra, Patra, Schadschneider, Chowdhury (2017)




Ghosh, Mishra, Patra, Schadschneider, Chowdhury (2017)




Ghosh, Mishra, Patra, Schadschneider, Chowdhury (2017)



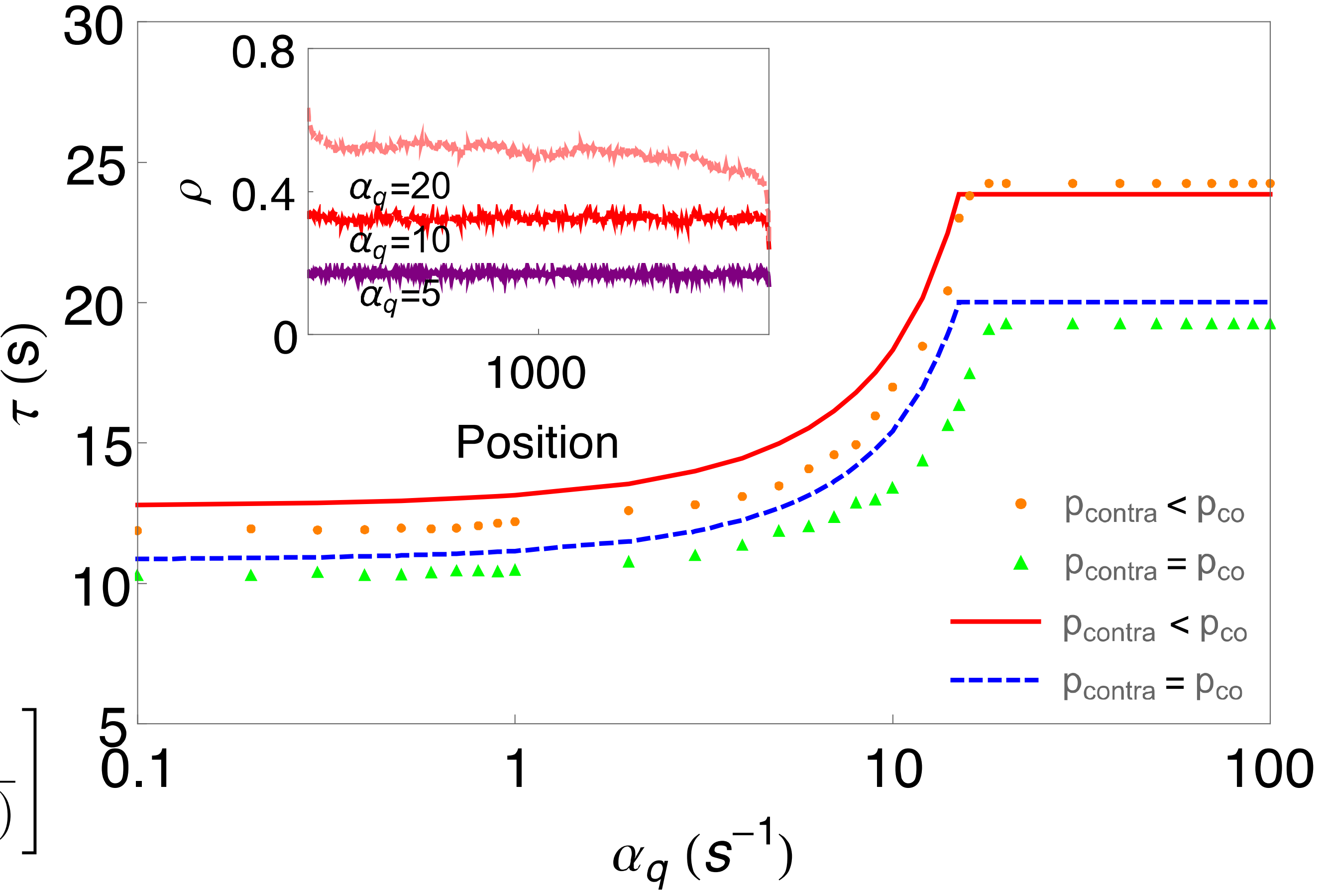
Ghosh, Mishra, Patra, Schadschneider, Chowdhury (2017)

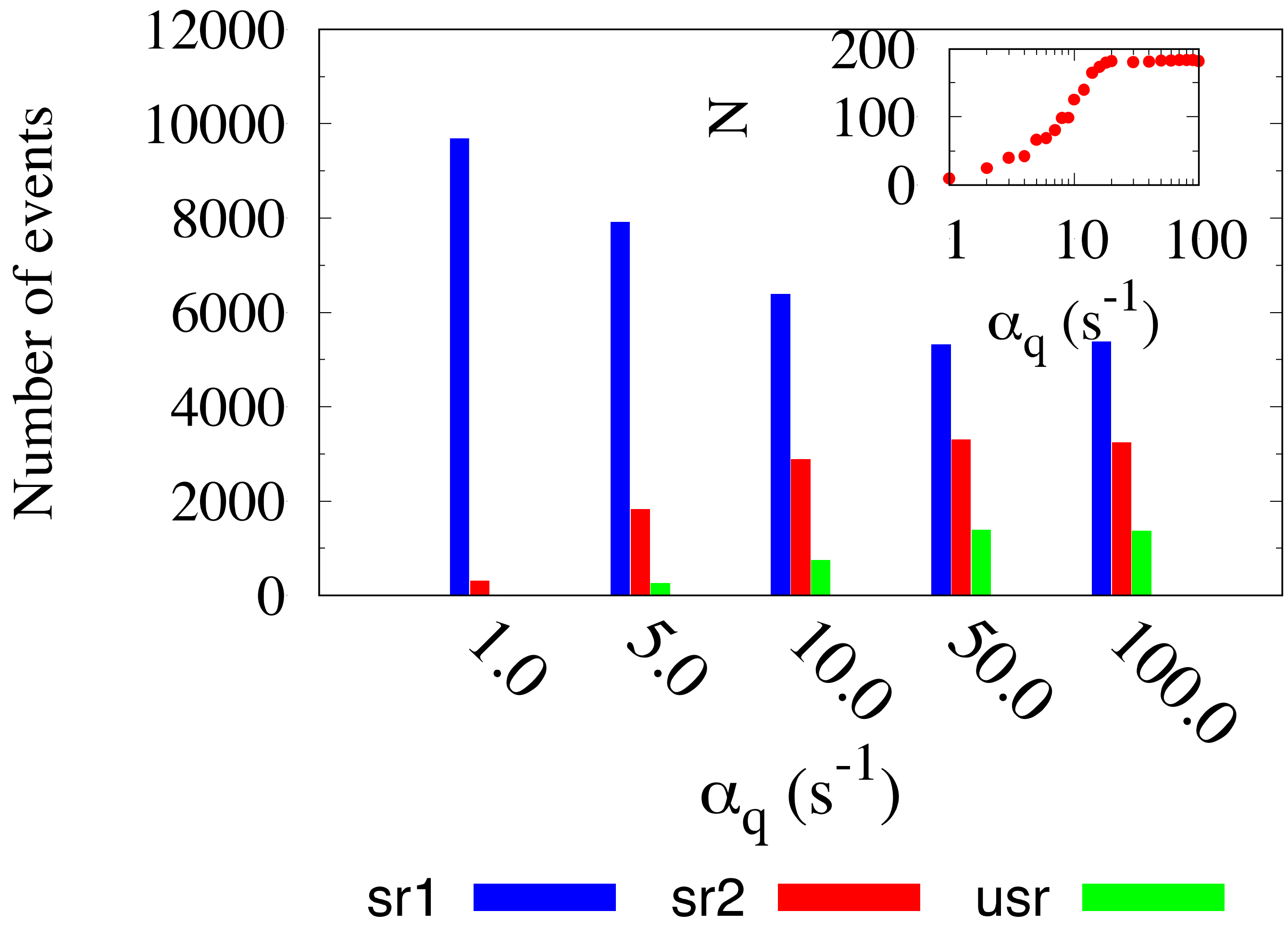
## Effect of Transcription on Replication

$$\tau = \frac{\tau_{int}}{2} + \frac{L}{4B_1}$$
$$= \frac{\rho L}{8}\left(\tau_{co} + \tau_{contra}\right) + \frac{L}{4B_1},$$

$$\tau_{co} = \frac{d}{v_{R_\ell} - v_P}$$
$$= \frac{1}{2\rho}\left[\frac{1}{B_1(1-\rho) - q(1-\rho)} + \frac{1}{p_{co}(1-\rho) - q(1-\rho)}\right]$$

$$\tau_{contra} = \frac{d}{v_{R_r} + v_P}$$
$$= \frac{1}{2\rho}\left[\frac{1}{B_2(1-\rho) + q(1-\rho)} + \frac{1}{p_{co}(1-\rho) + q(1-\rho)}\right]$$






Effect of Transcription on Replication

Ghosh, Mishra, Patra, Schadschneider, Chowdhury (2017)

# Ribosome Drop-off Model

Bonnin, Kern, Young, Stansfield, Romano, PLoS Comp. Biol. (2017)

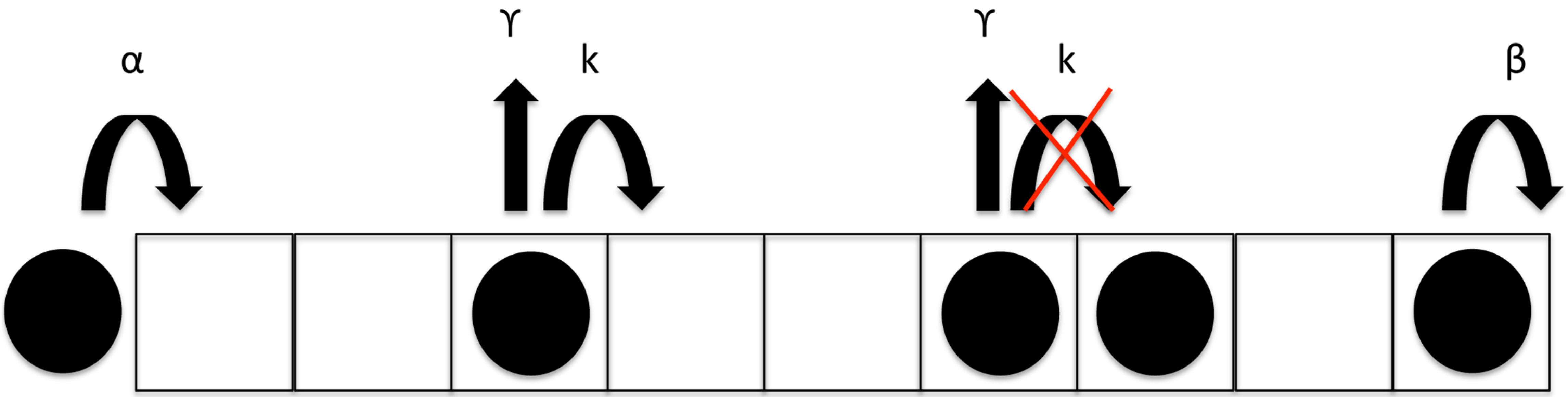
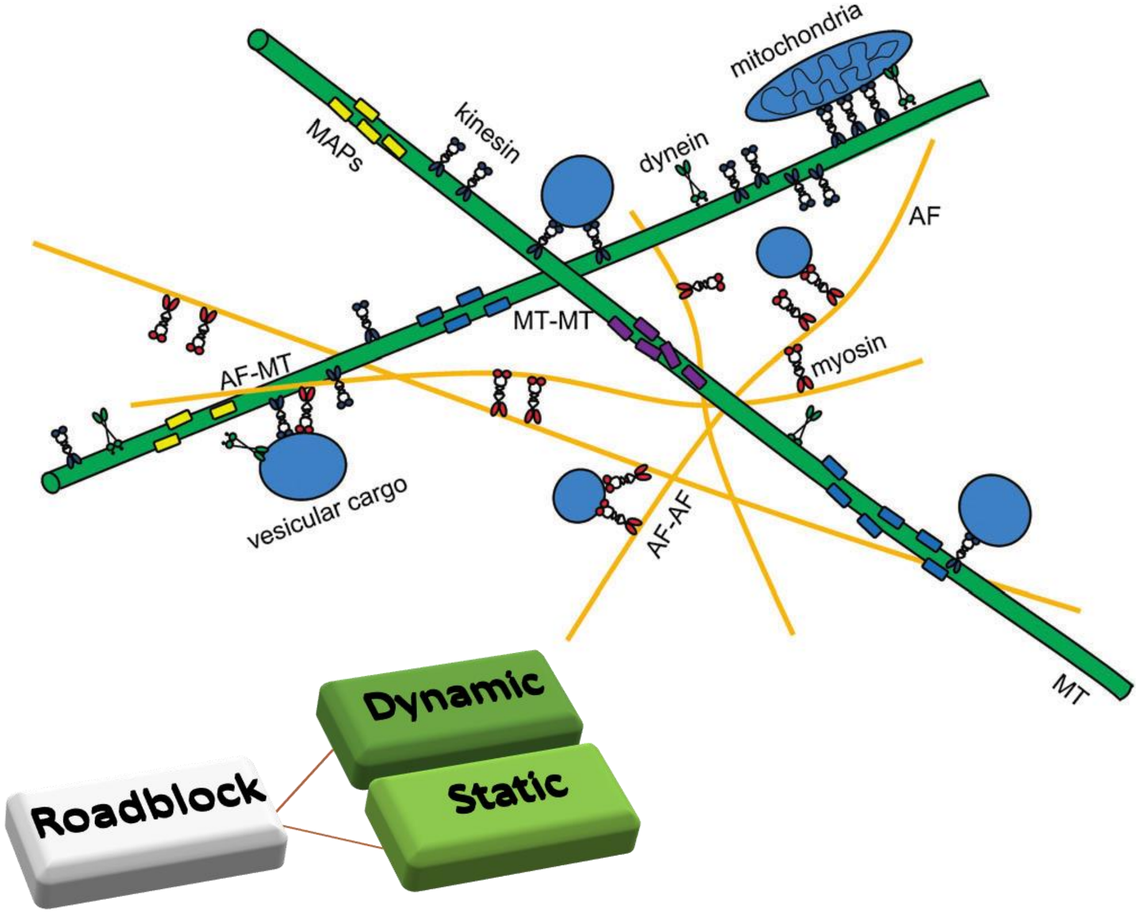
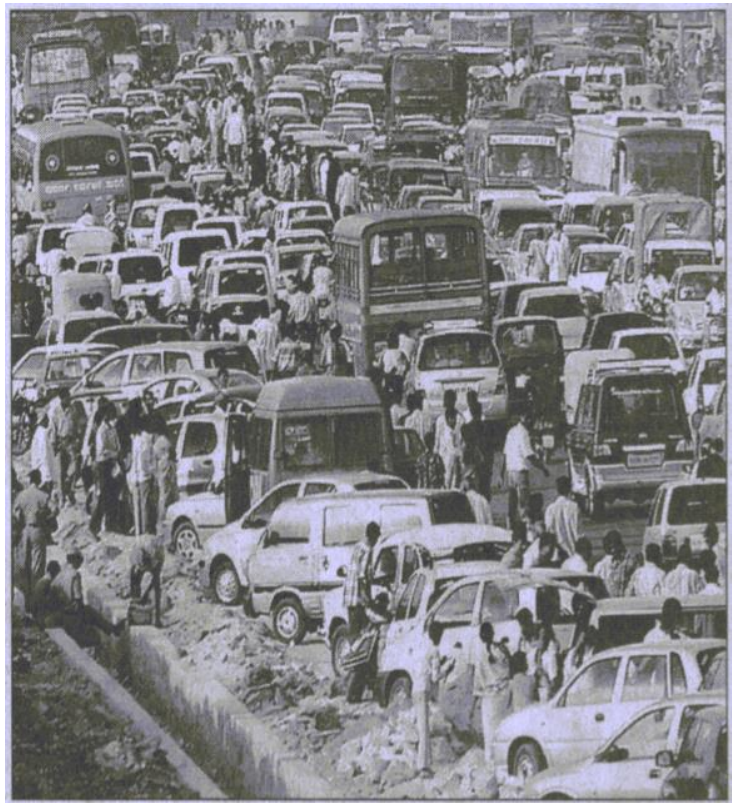



**Fig 2. Illustration of the ribosome drop-off model.** Ribosomes bind to the first codon of the mRNA with rate $\alpha$ and leave the lattice representing the mRNA strand at the stop codon, with rate $\beta$. Throughout the mRNA lattice they can either hop to the next codon, if it is free, with rate $k$, or drop off the lattice with rate $\gamma$.

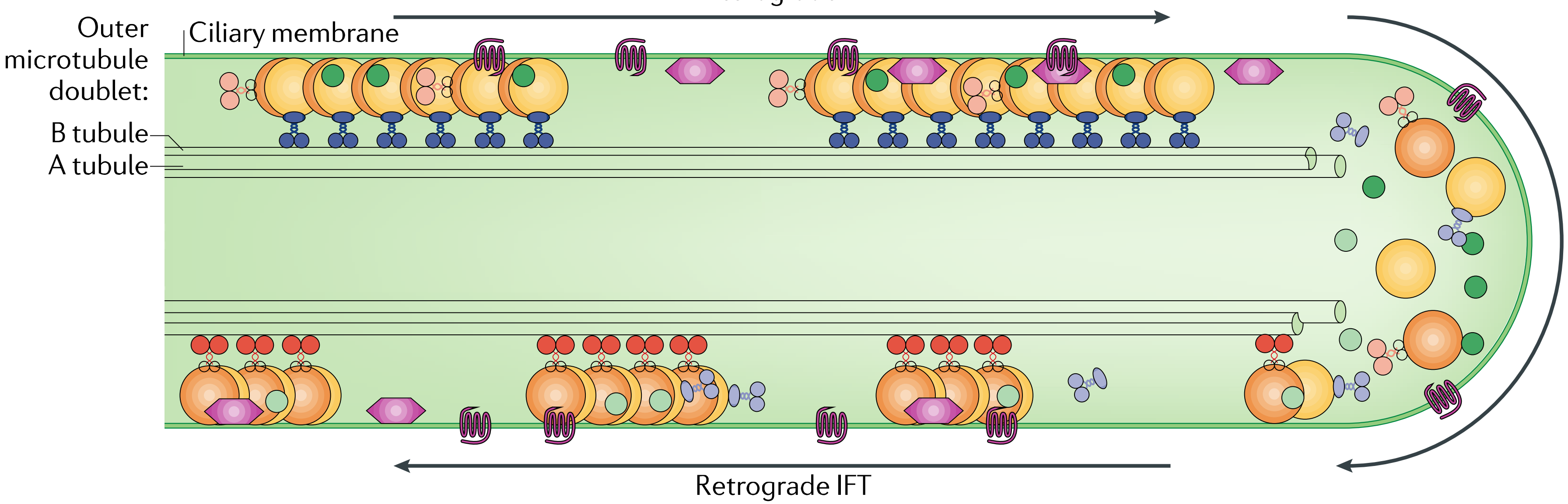
*"Like cities, cells have developed diverse transport systems to ensure that the right components are delivered to, or manufactured at, the right location at the right time. What are these transport systems? What are the intracellular roads or tracks, what are the engines and motors, and how do they operate? How are the various types of cargo shipped, and how is such transport tailored to demand? What determines whether it is the finished product that is shipped, or rather smaller parts or subunits for local on-site assembly? How are such mechanisms regulated to maintain cellular function, react to physiological stimuli, and ensure flexible adaptation to changing environments?"* Tiedge et al., PNAS (2001)



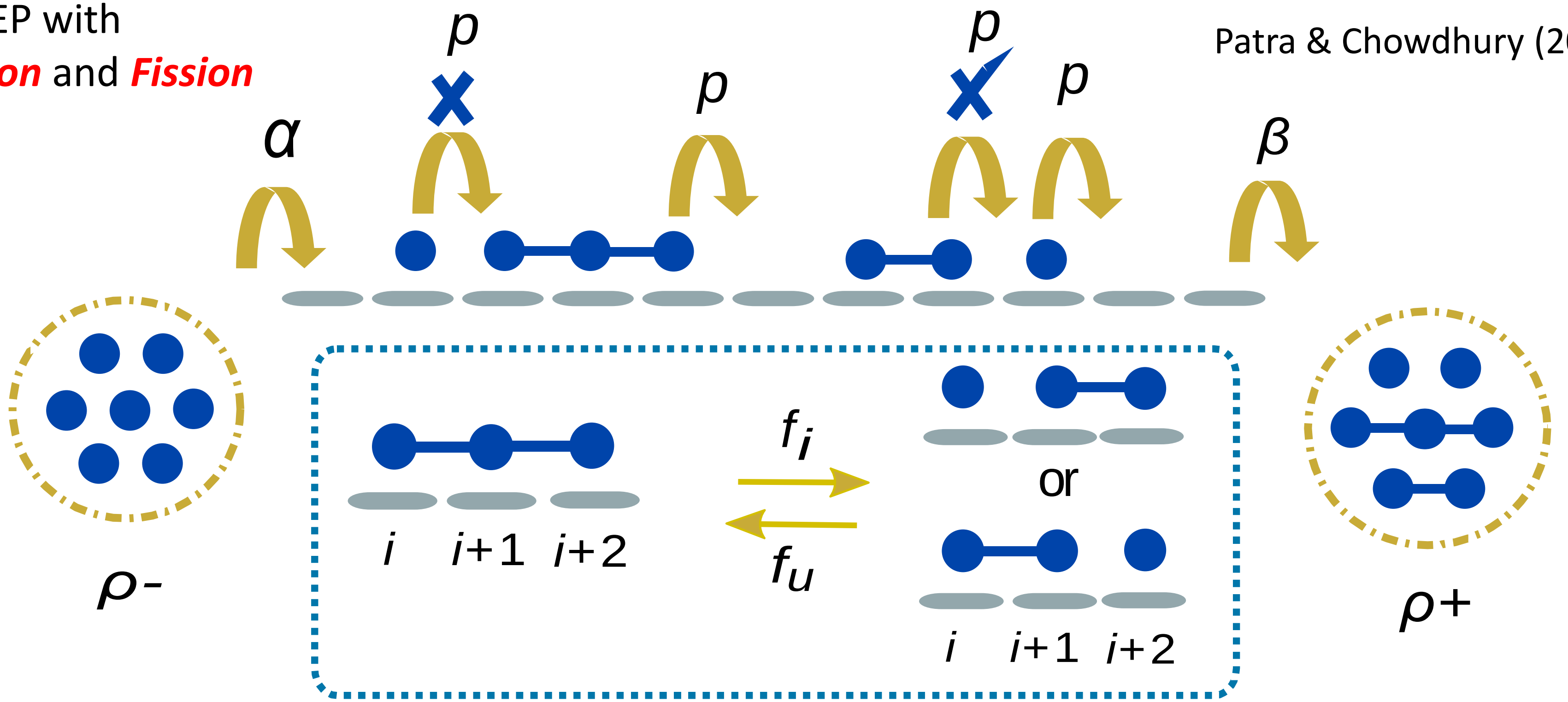
Times of India, Feb 16 (2007)

# Intraflagellar Transport (IFT)




TASEP with *Fusion* and *Fission*

Patra & Chowdhury (2017)



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