

A Discontinuous Galerkin FEM Approach for Simulation of a Model Describing Transcription in Ribosomal RNA

Davis, Gedeon, Gedeon & Thorenson

Department of Mathematical Sciences
Montana State University
Bozeman, MT

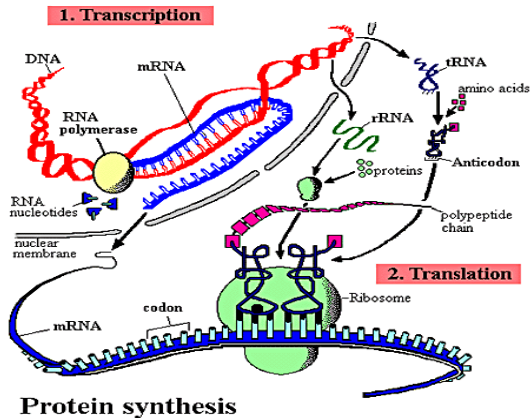
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Outline

- 1 Three Transcription Models
- 2 Numerical Simulations
- 3 Summary & References

Transcription, Translation and Protein Synthesis

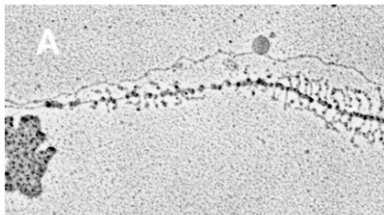
Transcription - the process of transferring genetic information from DNA to mRNA by RNA polymerase



- complex motion of RNAPs
- transcription factors
- density of RNAPs

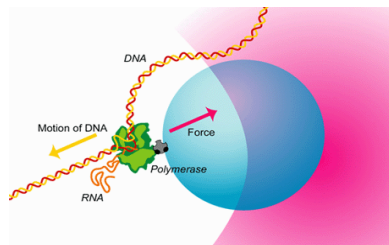
Experimental Observations

[Quan, et. al 2005] and [Block, et. al 2003]



Snapshots of rrn operon from a wild-type strain, compared with mutants (J. Bact.)

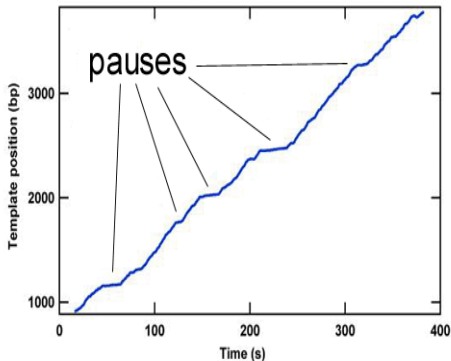
Block measures forces to get velocity estimates.
(Cell)



Transcriptional Pausing in E. coli

[Block, 2003]

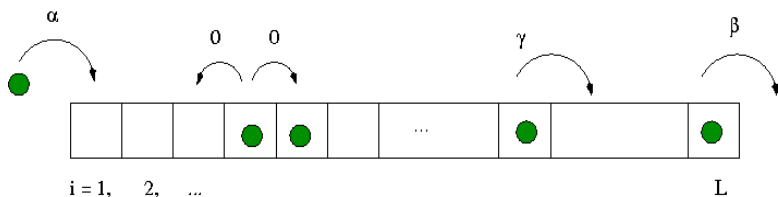
- RNAP transcribes DNA discontinuously, with periods of rapid nucleotide addition punctuated by frequent **PAUSES** (traffic lights)
- 3 Types of pauses: Short pauses vs. backtracking vs. hairpin pauses
- Average duration of Pauses: 1.2 secs (short) or 6 secs (longer).



(from Block's webpage)

Stochastic Model

[Chou and Lakatos, 2004] and [Zia, et. al, 2011]



- TASEP - Totally Asymmetric Simple Exclusion Process
- Lots of Analysis available when all hopping rates are equal. But when $\gamma = \gamma_i$ depends on the spatial location, then the long term behavior is less clear. Current depends on locations of pauses!
- Computer Simulations are possible. (Python Code)
- Does not account for length of RNAP

A Linear PDE Model

From [Silber, et.al 2010]

$$\partial_t(z(s, t)) + \partial_s(\beta(s, t)z(s, t)) = 0 \quad \text{for } 0 < s < L, t > 0$$

- Derived from microscopic model - a system of ODEs first considered by Heinrich & Rapoport, 1980. (and MacDonald & Gibbs, 1968)
- Assumes parameters of the system vary on a slower time scale than the time of RNAP transition between neighboring sites; Means that $\beta(s, t)$ varies slowly with s
- Distribution of RNAP along DNA is slowly varying about some equilibrium

We Propose a Nonlinear PDE Model

From Lighthill, Whitham(1955) & Richards(1956)

- From LWR model for traffic flow
- Assumes the flow velocity depends on density
 $v = v_{max}(x, t)(1 - z)$. So RNAP velocity is affected by the number of RNAP transcribing the DNA strand.
- Allows for shock waves to form.
- No mechanism for a polymerase to anticipate the movements of those RNAP that are downstream.

$$\begin{aligned}z_t + [v_{max}(x, t)(1 - z)z]_x &= 0 & x \in (-0.5, 0.5), & t > 0 \\z(x, 0) &= z_0 \\z(-0.5, t) &= z_0\end{aligned}$$

v_{max} is instantaneous transcription rate

Traffic Flow After a Red Light Turns Green

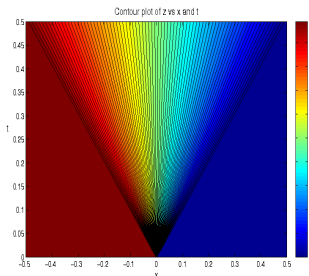
Smooth flux but piecewise constant initial data, $O(h)$ convergence (Hesthaven)

$$\text{Solving } z_t + [(1-z)z]_x = 0 \quad x \in (-0.5, 0.5), \quad t > 0$$

$$z(t, -0.5) = 1, \quad z(x, 0) = \begin{cases} 1 & x < 0 \\ 0 & x > 0 \end{cases}$$

Closed form solution

$$z(x, t) = \begin{cases} 1 & \text{if } x < -t \\ \frac{1}{2} - \frac{x}{2t}, & \text{if } -t \leq x \leq t \\ 0 & \text{if } x > t \end{cases}$$



# of elements	$L^2(-0.45, 0.45)$ Error	order
40	0.0125731	
80	0.0063915	0.9761
160	0.0032297	0.9847
320	0.0016262	0.9898
640	0.0008183	0.9908
1280	0.0004134	0.9850

- Linear basis Functions
- L^2 Error at final time $T = 0.5$
- **Boundary Conditions Matter for $O(h)$ convergence!**

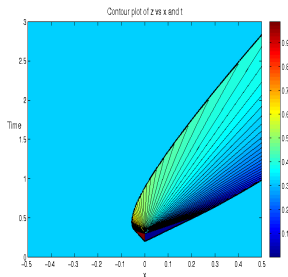
Transcription with a Single Pause

Traffic with One Red Light

$$z_t + (\beta_{\max}(x, t) (1 - z) z)_x = 0 \quad x \in (-0.5, 0.5), \quad t > 0$$

$$z(x, 0) = 0.31$$

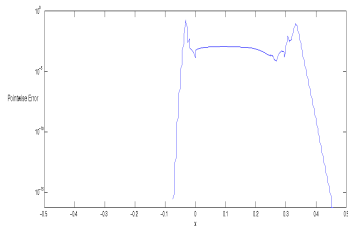
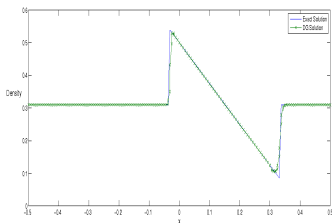
$$z(-0.5, t) = 0.31 \quad \text{Relevant to RNAP}$$



$$\beta_{\max}(x, t) = \begin{cases} 0 & x = 0; \quad t_1 < t < t_2 \\ 1 & \text{otherwise} \end{cases}$$

Accuracy of Numerical Simulation

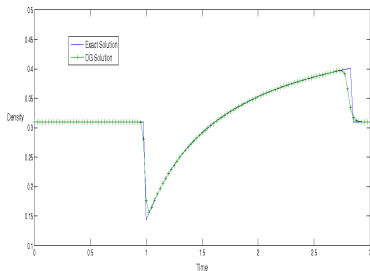
Convergence?



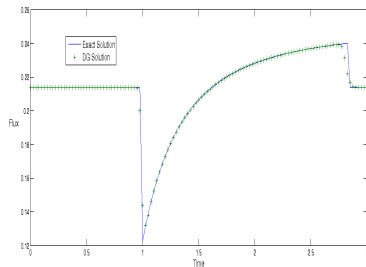
- Solution and Pointwise Error at $T = 0.7$ using 160 elements
- Slope Limiter smooths corners and avoids oscillations for stability
- No Clear Cut Convergence Rate

# of elements	$L^2(-0.5, 0.5)$ Error	order
40	0.0272855	
80	0.0132250	1.04
160	0.0037195	1.83
320	0.0003236	3.52
640	0.0001836	0.82
1280	0.0000767	1.26

Density and Flux Calculations at Termination Site



(a) Density at $x = 0.5$



(b) Flux at $x = 0.5$

Figure: DG and true solution using 160 elements

Quantifying the Delay

How do pauses affect crossing time?

- No pauses and $z(-0.5, t) = z_0 \Rightarrow$ constant $z = z_0$ and $f_R = (1 - z_0)z_0$
- With this constant flux f_R , the amount of polymerases to reach termination over time interval (t_0, T) is

$$N = \int_{t_0}^T f_R dy = f_R(T - t_0)$$

- Assuming RNAPs pause, define $s(t)$ to be the instant of time such that

$$\int_{t_0}^{s(t)} f(z(0.5, w)) dw = f_R(t - t_0)$$

- $s(t)$ describes the amount of delay the RNAPs experience.
- The average delay is defined by

$$d = \frac{\int_{t_0}^T f(z(0.5, t))(s(t) - t) dt}{\int_{t_0}^T f(z(0.5, t)) dt}$$

Numerical Approximations of the Delay

Average Delay for One Pause Model

- Calculations for $z_0 = .31$
- Used Composite Trapezoidal Rule for the Numerical Integration
- Using exact expression for flux, the exact value of delay is $D = 0.041419$

# of elements	DGFEM delay d	Error $ D - d $
40	0.03077134	0.01069098
80	0.03657621	0.00488611
160	0.03901747	0.00244486
320	0.04013111	0.00133122
640	0.04063800	0.00082432
1280	0.04104258	0.00041975

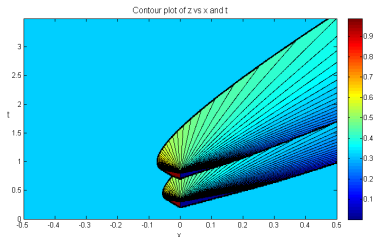
Two Pause Model

Two Pauses with time between pauses parameterized

Same PDE, IC and BC with

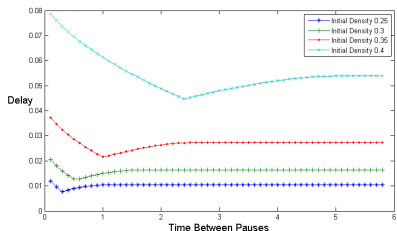
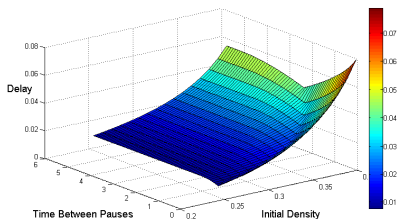
$$\beta(x, t) = \begin{cases} 0 & x = 0; \quad 0.2 < t < 0.3 \quad \text{or} \quad 0.4 + i < t < 0.5 + i \\ 1 & \text{otherwise} \end{cases}$$

where $i = 0.1, 0.2, \dots$, N increases the time between pauses.



- Contour Plot is for one DG simulation
- Both pause durations are 0.1 units of time
- Pause 1 - begins at $t = 0.1$
- Pause 2 - begins at $t = 0.7$

Delay Calculation for Two Pause Model

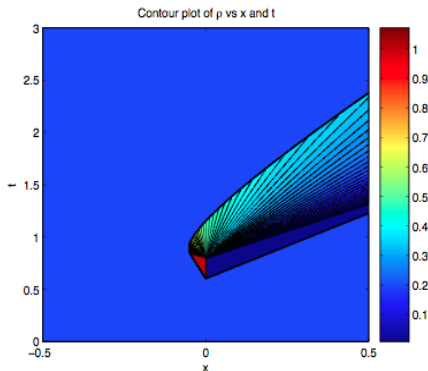


- Surface plot of delay for various initial densities 0.25-0.4 and time between pauses 0.1-5 time units.

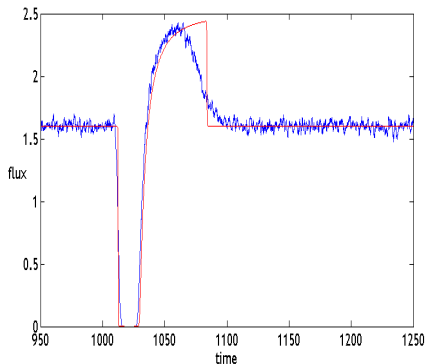
- Cross sections of delay plot showing a minimum in the delay for each initial density.

Compare Nonlinear PDE and Stochastic Models

DGFEM in Matlab[Hesthaven] for PDE and Python[Gedeon] for Stochastic Model



Contour plot of density using DGFEM solver with pause of length 0.2 time units.



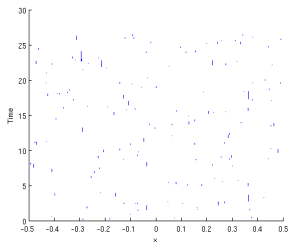
Flux Along Termination Site
 DGFEM Solution and Stochastic Model

Incorporating a Distribution of Multiple Pauses

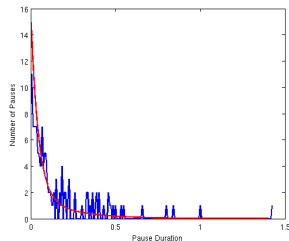
Time Duration is Double Exponential Distribution - Block (2003)

To model the i^{th} pause at location $x = L_i$ with start time t_{s_i} and duration d_i , use the function

$$v_{\max}(x, t) = \begin{cases} 0 & x = L_i; \quad t_s < t < t_s + d_i \\ 1 & \text{otherwise} \end{cases} \quad \text{for } i = 1, 2, \dots, M$$



Location and duration of 146 pauses
Uniformly distributed in space

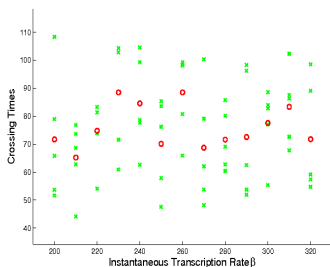


Double Exponential Distribution
Durations: 1.2 ± 0.1 secs (60%) and
 6.0 ± 0.4 secs (40%)

Average Crossing Times Experienced by RNAP

[Klump & Hwa, 2008], [Dennis, et. al 2009] rrn operon specific data

- Assume transcription rate is *roughly constant* between pauses
- Estimate the **instantaneous transcription rate β** that results in a crossing time of about 60 seconds if, on average, the RNAP encounters a pause every 10 seconds.
- Car velocity in the (un-scaled) traffic flow model is $\beta(1 - z)$
- Calculate Average Delay per RNAP
- Average Total Crossing Time = Avg. Crossing Time + Avg. Delay
- Investigate for many realizations of draws of pauses



Summary & Acknowledgements

Summary

- Three models and some implementations for transcription.








What's Next?

- Model does not account for RNAP length. Time-scaling improvements, and making it more biologically relevant.
- Sensitivity Analysis - How does flux at termination site depend on location and duration of the pause in the One-Pause model?


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