Outline of the series

- Overview/Review "Equilibrium SM *vs.* Nonequilibrium SM"
- An Ising-like model in DDS "Shattered expectations"
- DDS in one-dimension "Bare bones NESM"
  - Interesting physics, despite just 1-D and "no interactions"
  - Potential applications - protein synthesis
  - Exact solutions and intractable extensions
- Systems with more than one driven species "American football, Barber poles, and Clouds"
- Summary and Outlook "Come and join in the fun!"

Driven Ising Lattice Gas

The surprises continue…

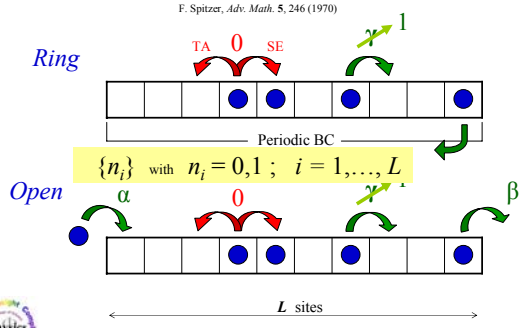
- $E = 0$ $J \neq 0$ $d = 1,2$ (Lenz-Ising, Onsager, Lee-Yang, …)
- $E > 0$ $J > 0$ $d = 2$ KLS
- $E > 0$ $J = 0$ $d = 1$ Asymmetric Simple Exclusion Process
- $E = \infty$ $J = 0$ $d = 1$ Totally ASEP (Spitzer 1970)
  - for PBC, P^* trivial, but dynamics non-trivial
  - for OBC, P^* non-trivial ("boundary induced" phases)
  - for OBC, dynamics even more exciting
  - extensions (still $E=\infty$ $J = 0$) for modeling protein synthesis

Outline of TASEP's

- Brief glimpse of "early" TASEP's
  - What's TASEP? - a "toy in pure mathematics" (1970)
  - A chemist's model for protein synthesis - the 1968&69 studies
- Physicists' TASEP
  - Phase transitions in 1-D, density profiles, anomalous diffusion…
  - Exact solutions and their limitations (for finding e.g., a simple quantity)
- Extensions motivated by protein synthesis
  - TASEP is too "simple" indeed
  - Effects of extended objects (particles covering more than one site)
  - Effects of inhomogeneities and their locations
  - Effects of competition with other TASEPs

Mathematician's TASEP

F. Spitzer, *Adv. Math.* **5**, 246 (1970)



Questions of interest

- What is stationary distribution: $P^*(n_i)$?
- What can we say about the t dependence: $P(n_i,t)$?

Biochemist's TASEP

Working independently of, and most likely simultaneously as F. Spitzer,

J. H. Gibbs, a chemist + A. C. Pipkin, an applied mathematician

studied a model for ***protein synthesis***.

This study formed the PhD thesis of

C. T. MacDonald

at Brown, and published as two papers:

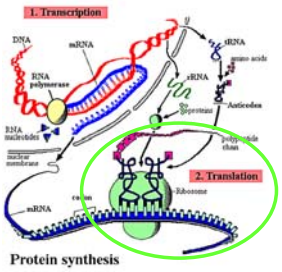
C.T. MacDonald, J.H. Gibbs, and A.C. Pipkin, *Biopolymers* (1968+69)

… brief detour into biology

Brief detour …"Central Dogma"

- DNA ~1G base-pairs; 2% codes for ~25K genes
- RNA Many many types: mRNA, tRNA, rRNA, …
- mRNA 10-3K codons, makes
- Proteins
  - a string of amino-acids (an aa-chain), known as "polypeptide chain"
  - folds to have specific function
  - e.g., keratin (nail, hair), hemoglobin, receptor protein (nerve), ompA, …

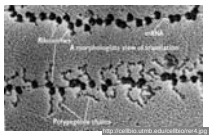
translation



A ribosome…

- starts at one end (initiation)
- goes to the other, "knitting" the aa-chain (elongation)
- releases aa-chain at the end and falls off mRNA (termination)

Before one falls off, another one starts!



(some) Questions of interest

- What is production rate in steady state?
  - related to protein levels assuming constant degradation rate
  - given by TASEP current J in steady state
- What can we say about the overall occupation and density profile ?
  - of interest to competition ??
- Full dynamics is far, far down the present priority list!

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  - Exact solutions and their limitations (for finding e.g., a simple quantity)
- Extensions motivated by protein synthesis
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  - Effects of extended objects (particles covering more than one site)
  - Effects of inhomogeneities and their locations
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Questions for TASEP

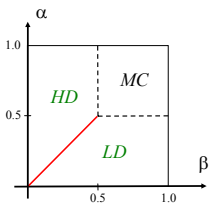
- What is stationary distribution: $P^*(n_i)$?
- What is full dynamics $P(n_i,t)$?

(some) Answers for TASEP

- What is stationary distribution: $P^*(n_i)$?
- What is full dynamics $P(n_i,t)$?
- For the *Ring*, $P^* \propto 1$ (Spitzer, 1970; "pairwise DB")
- but with non-trivial dynamics
- For the *Open case*, P^* non-trivial (1992)
- with even more interesting dynamics

The Open TASEP

3 phases: *M*ax *C*urrent, *H*igh/*L*ow *D*ensity



MC: average density ≡ ρ = 0.5

HD/LD: ρ = 1–β > 0.5 / ρ = α < 0.5

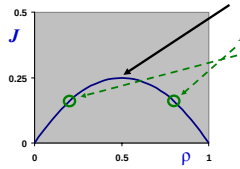
---- continuous ("second order") transition

—— discontinuous transition; coexistence of *HD/LD* regions; sharp interface; shock "phase" *SP*

underlying particle-hole symmetry: α ⇔ β & ρ ⇔ ρ_h =1–ρ

The Open TASEP

3 phases: *M*ax *C*urrent, *H*igh/*L*ow *D*ensity



MC: average density ≡ ρ = 0.5

HD/LD: ρ = 1–β > 0.5 / ρ = α < 0.5

In all cases, simple relationship between current, ***J***, and ρ exists:

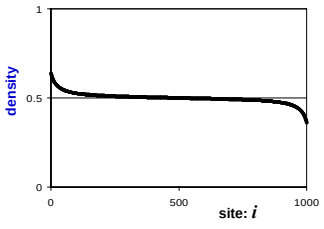
$$J = \rho\rho_h = \rho(1-\rho)$$

where $\rho_h \equiv$ *hole* density = 1 – ρ

(exact, though MF-like)

The Open TASEP

Typical profiles: *MC*

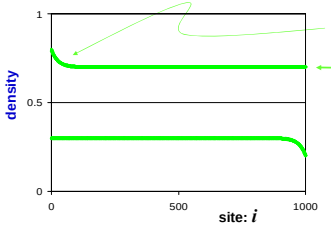


"tangent" in MF

anomalous algebraic decay into bulk… 'critical'

The Open TASEP

Typical profiles: *HD/LD*



exaggerated tail, typically O(1)

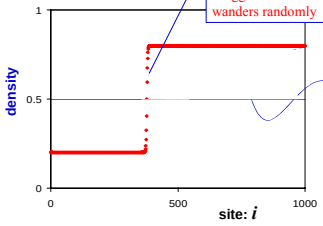
no tail at all here

non-critical, Gaussians

The Open TASEP

Typical profiles: *SP*

"shock" (or "domain wall") : exaggerated interface width, typically O(1); wanders randomly



The Open TASEP

- Much, much more is known ***exactly***:
  - fluctuations and correlations, average ***J***, anomalous dynamics, shock properties, etc.
  - using mapping to quantum chain, Bethe ansatz, and "matrix product" methods (reviews by G.M. Schütz, Evans, Derrida, Mallick,…).
  - lots of hard work, just to get (Bethe ansatz) *equations* for spectrum and eigenvectors!
- Exact solutions have limitations:
  - very specialized (cannot be generalized, even for "small" changes)
  - ditto (even for "simple" quantities, such as …)

Total Occupation in Open TASEP

- A simple, natural question:
- The stationary properties (e.g., average, fluctuations) of the total occupation, N, are known…
- What about its time dependence $N(t)$? (i.e., correlations in time)
- …especially for ***finite*** systems?
- Motivations come from biology.

Motivations from biology

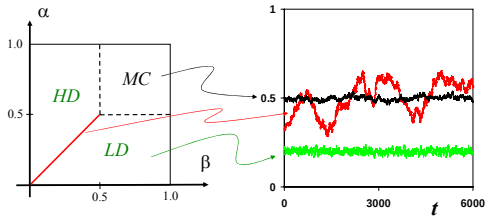
Many (copies of many different) mRNA's ***compete*** for one pool of ribosomes (and aa-tRNA's).

- Do some "win big" and others "lose out"?
- To quantify these, need $N_i(t)$ or their FT's.
- Baseline study: What's $N(t)$ like, for just *one* TASEP ?

...especially for ***finite*** L !

Total Occupation in Open TASEP

$N(t)/L$



$L = 1000$; $t_{\text{unit}} = 100$MCS

Power Spectra of Total Occupation

$I(\omega) \equiv \langle\, |\widetilde{N}(\omega)|^2 \,\rangle$

Can be predicted, *in principle*, through the ***exact solution***.

But, ***in practice***, need

- the entire spectrum,
- special linear combinations of … ***all*** the eigenvectors,
- sum over the above!

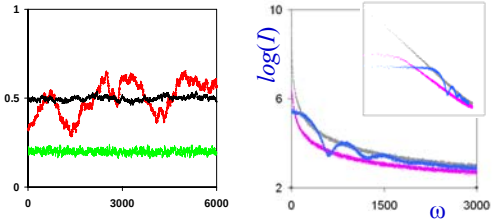
To be precise:

- take 10^8 MCS in steady state
- measure N every 100 MCS
- have 10^6 measurements
- cut into 100 samples of…
- 10^4 N's and get $\widetilde{N}$
- average over the 100 samples

D. Adams, R.K.P. Zia, and B. Schmittmann PRL **99**, 020601 (2007)

Power Spectra of Total Occupation

$I(\omega) \equiv \langle\, |\widetilde{N}(\omega)|^2 \,\rangle$



- Oscillations generic (for finite L!):
  - Toy: single particle, constant v, random entrances
  - Effect of dispersion/diffusion: filling in minima
- Simple minded, linearized Langevin equation:

$$\partial_t \rho = D\partial^2\rho - \partial\left[\rho(1-\rho)\right] + \partial\eta \qquad \langle \eta(x,t)\eta(x',t')\rangle \propto \delta(x-x')\delta(t-t')$$

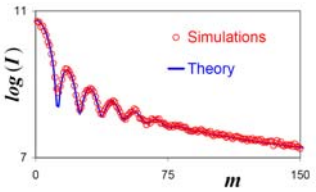
$$\rho = \bar{\rho} + \varphi$$

biased diffusion, conserved noise

$$\boxed{\partial_t \varphi = D\partial^2\varphi - v\partial\varphi + \partial\eta} \qquad v \equiv 1 - 2\rho$$

$$N(t) = \int_0^L \rho(x,t)\,dx \;\Rightarrow\; \widetilde{N}(\omega) = \int_k (e^{ikL} - 1)\,\frac{\widetilde{\eta}(k,\omega)}{Dk^2 + ivk - i\omega}$$

some answers & puzzles



$L = 32000$ $\alpha = 1-\beta = 0.3$

$L = 32000$ $v = 0.4$ $(\rho=\alpha)$

$D = 20$ $A = 500$

Outline of TASEP bit

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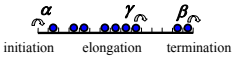
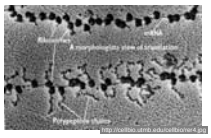
Extensions (motivated by) protein synthesis

MacDonald, Gibbs, and Pipkin, *Biopolymers* (1968+69)

- To model translation in protein synthesis…
  where ribosomes bind to the mRNA,
  move along "reading" a string codons, and
  detach at the end,
- Gibbs introduced a 1-d lattice for the mRNA with
  site ⇔ codon particle ⇔ ribosome



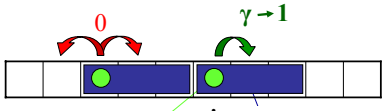


Extensions (motivated by) protein synthesis

- But, many aspects of TASEP are too Simple!
- Here, let's focus on just *three* extensions:
  - A ribosome is a large molecule covering typically 10-12 codons, so our TASEP particles need to be *extended objects* covering ℓ (=12 mostly) sites
  - Inhomogeneous jump rates
  - Competition for finite resources

Gibbs & co. had these in '68+'69!

TASEP with Extended Objects



System's configuration specified by reader occupation: $\{r_i\}$; $r_i = 0,1$

NOT all $\{r_i\}$'s allowed!!

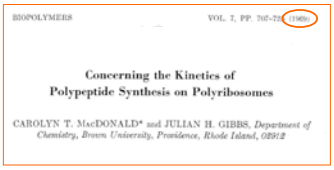
"Reader" reading codon at site ***i***
(chosen arbitrarily at the "end")

Ribosome "covering" ℓ (=3 in this illustration) codons

Open TASEP with extended objects first considered by

J. H. Gibbs

MacDonald's PhD thesis 1968, 1969



good MFT for extended objects on ***open*** chain…

…solved numerically, mostly for $\ell = 2$

$J = \langle r_i(1-r_{i+\ell})\rangle \to \langle r_i\rangle\langle 1-r_{i+\ell}\rangle$ *very poor*; except for $\ell=1$. MGP more sophisticated

TASEP with Extended Objects

*...on a homogeneous **Ring*** : $\gamma = 1$

- $P^* \propto 1$ still holds…
- every configuration mapped to $\ell = 1$ case

  …with a smaller ring: $L - (\ell - 1)M$

  M = the number of ribosomes

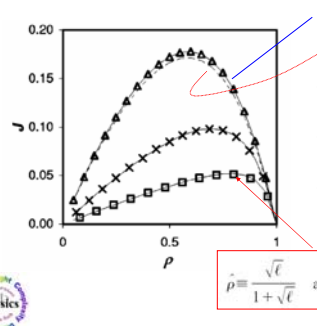
TASEP with Extended Objects

Homogeneous Ring: $\gamma_i = 1$

Yet, there are interesting aspects:

- two different overall densities:
  - ✓ "coverage": $\rho = 1 - $ *hole* density $\equiv 1 - \rho_h$ $\in [0,1]$
  - ✓ "reader": $\rho_r =$ *particle* density $= M/L = \rho/\ell$ $\in [0, 1/\ell]$
- current-density: $J(\rho) = \rho_r \rho_h / (\rho_r + \rho_h)$
- non-zero, amusing *r-r* correlations!

TASEP with Extended Objects



exact, with Finite Size Effects

$\rho_r \rho_h / (\rho_r + \rho_h)$

$\ell = 2$ in $L = 40$

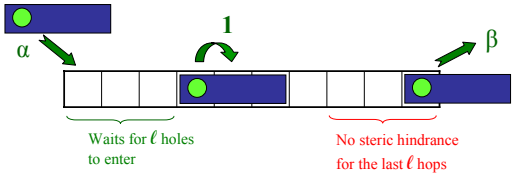
$\ell = 5$ in $L = 80$

$\ell = 12$ in $L = 150$

$\hat{\rho} \equiv \frac{\sqrt{\ell}}{1+\sqrt{\ell}}$ and $\hat{J} \equiv (1+\sqrt{\ell})^{-2}$

TASEP with Extended Objects

*Homogeneous **Open Lattice***: $\gamma_i = 1$; α; β



Waits for ℓ holes to enter

No steric hindrance for the last ℓ hops

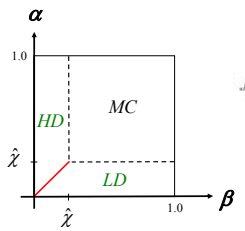
Lakatos and Chou, JPA **36**, 2027 (2003): "complete entry" and "incremental exit"

Rules differ if "reader" placed elsewhere, but physics remains the same!

TASEP with Extended Objects

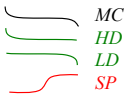
Homogeneous Open Lattice: $\gamma_i = 1$; α; β

- $P^* = ???$
- mapping to ℓ=1 case ***not*** simple
- many new interesting aspects:
  - phase diagram and currents modified
  - new features in density profiles
    - expected: different ones for $(\rho_{reader})_i$ *vs.* ρ_i
    - expected: period ℓ structures
    - somewhat unexpected: ***very long*** tails (***none*** for $\ell = 1$)
    - completely unexpected: yet to be discovered!



$$J(\alpha,\beta) = \begin{cases} \frac{\alpha(1-\alpha)}{1+\alpha(\ell-1)} & LD \\ \frac{\beta(1-\beta)}{1+\beta(\ell-1)} & HD \\ \hat{j} & MC \end{cases}$$

Profiles same, but only ***qualitatively***:



But, simulations show ***serious quantitative*** differences…

Gibbs & co. had these!

Recap of 1st Extension

Homogeneous TASEP's with ***extended objects*** are qualitatively similar to the ℓ=1 case, but…

- ***Ring:*** Though P^*=1,
  - there are non-trivial *r-r* correlations
- ***Open:*** P^* = ???
  - phase diagram and $J(\rho)$ modified
  - novel features in density profiles

Extensions (motivated by) protein synthesis

- But, many aspects of TASEP are too Simple!
- Here, let's focus on just *three* extensions:
  - ~~Extended objects~~
  - 61 codons ⇔ 61 aa-tRNA's, with widely varying concentrations. Ribosome waiting times may differ, so we should have ***site-dependent jump rates***:

    $\{ \gamma_i \neq 1 \}$
  - ~~Competition for finite resources~~

Gibbs didn't have these.

TASEP with *e*xtended objects and *i*nhomogeneous rates

TASEP → TA*i*S*e*EP

definitely ***NOT*** simple

TA*i*S*e*EP

Inhomogeneous Open Lattice: α ; γ_i ; β

- full problem of "*quenched randomness*"

  Harris and Stinchcombe (ℓ=1), PRE **70**, 016108 (2004)

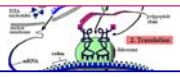
  …every γ_i from the same distribution (e.g., Gaussian); our case even ***more complex***
- Why study such a hard problem?
- Again, motivations from biology…

  …worse, *q.r.* averages may not be meaningful
- Indeed, there is a ***new type*** of problem: "Quenched distribution of distributions"

A little more detail…

… how does the ribosome move from codon to codon?

This leads us to consider $\{\gamma_i\}$!!



To advance, the ribosome must wait for the arrival of the appropriate aa-tRNA.

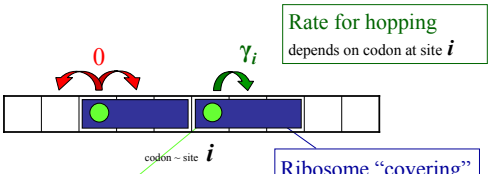
aa-tRNA concentrations [aa-tRNA] may vary greatly, so that the waiting times can differ seriously.

Our interests are many, e.g.,

Overall current, J, which controls protein levels and

Profiles, $(\rho_{reader})_i$, which controls which tRNA's are bound

TASeEP



TA*i*S*e*EP

Inhomogeneous Open Lattice: α ; γ_i ; β

- full *quenched randomness* is tough!
- start simply…study one/two γ's $\neq 1$
  - Fast ($\gamma > 1$) sites affect density profiles, but not J.
  - Slow ($\gamma < 1$) sites affect both.
  - Location of slow sites (e.g., clustering) is important.

Qualitative understanding from several mean field approaches:

Take two/three open TASEPs and match J across blockages

(details in DSZ, PRE76, 2007+JJD thesis)

Quantitative theory, good for all k's, still lacking

Recap of 2nd Extension

- Slow "sites" reduce overall current (hardly surprising!)
- Two equally slow sites…
  - far apart affect current like just one blockage
  - close together reduces current much more
- Possible implications for translation and/or designer genes, exploiting *synonymous codons*
- Example with *dnaA* (from *E. coli*) shows promise.
- How to deal with problem of "Quenched distribution of distributions"?

Extensions (motivated by) protein synthesis

- But, many aspects of TASEP are too Simple!
- Here, let's focus on just *three* extensions:
  - Extended objects
  - Inhomogeneous jump rates
  - Typical cells have many copies of many types of mRNA's, all using ribosomes (and aa-tRNA's) from the same pool, so we should study the effects of a ***finite reservoir of particles*** on one or more TASEP's.

David Adams Jon Cook

D. Adams, B. Schmittmann, and R.K.P. Zia JSTAT P06009 (2008)
L. J. Cook and R.K.P. Zia JSTAT P02012 (2009)
L. J. Cook, R. K. P. Zia, and B. Schmittmann arXiv: 0906.3730

Effects of finite resources

The supply of ribosomes in a cell is finite!

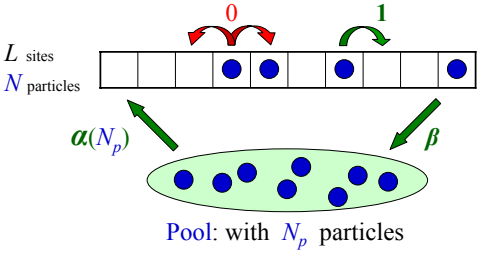
All mRNA's compete for this resource.

- Who "wins" and who "loses"?
- Should study many TASEP's competing for a pool of particles.

But, to begin with,

How does this affect a ***single*** TASEP?

Constrained TASEP



Pool: with N_p particles

Constrained TASEP

$N_{tot} = N + N_p$

is a ***fixed*** number of particles in the system (ribosomes in the cell)

We chose $\alpha(N_p) = \alpha\ tanh(N_p/N_\times)$

…numbers in TASEP feeds back to "on-rate", via N_{tot}-N

Some crossover scale, chosen as $\rho^* L$ so that we can "see" an effect easily.

An intrinsic "on (initiation) rate", if the supply were unlimited.

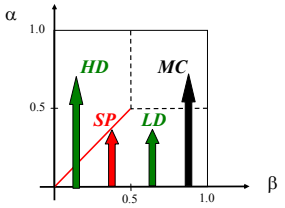
Constrained TASEP

- Summary of parameters and fixed choices:
  - L, α, β, N_{tot}
  - $N_\times$ ($=\rho^* L$), *tanh* function
- Regions studied: *MC, HD, LD*
- Quantities of interest, as N_{tot} is varied:
  - steady state current: J (protein levels in a cell)
  - total occupancy: N *or* $\rho \equiv N/L$

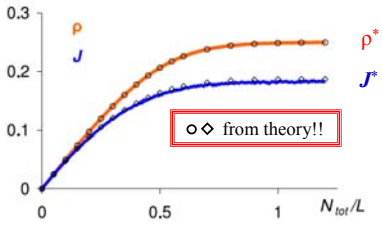
No * here!!! constrained TASEP

Constrained TASEP

Since the on-rate varies from 0 to α, the four possibilities, as N_{tot} increases from zero, are:



Constrained TASEP: *LD*



$\rho^* = 0.25$

$J^* = \rho^*(1-\rho^*)$

◇◇ from theory!!

LD: α=1/4, β=3/4, L=1000, $N_\times/L$=0.25

Constrained TASEP: *LD*

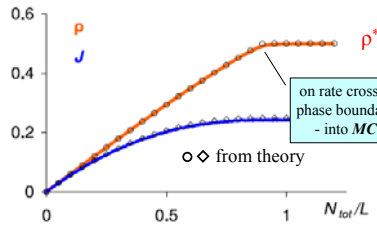
- In ordinary *LD* TASEP, we have $\rho^* = \alpha$; $N_\times = \alpha L$
- Set self-consistent condition:

$$\rho/\alpha = tanh(\rho_{tot}/\alpha - \rho/\alpha)$$

$$\rho \rightarrow \begin{cases} \rho_{tot}/2 & \rho_{tot} \rightarrow 0 \\ \alpha & \rho_{tot} \rightarrow \infty \end{cases} \qquad \rho_{tot} \equiv N_{tot}/L$$

- Current from the usual: $J = \rho(1-\rho)$

Constrained TASEP: *MC*



$\rho^* = 0.5$

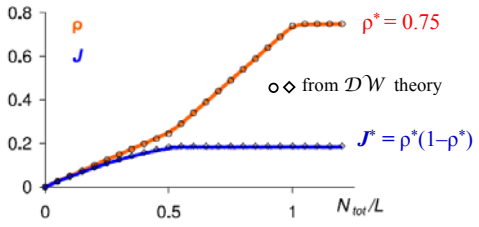
on rate crosses phase boundary - into ***MC***

0.25

◇◇ from theory

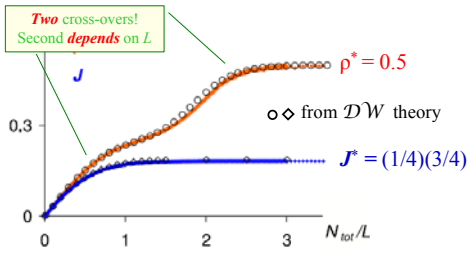
MC: α=3/4, β=3/4, L=1000, $N_\times/L$=0.5

Constrained TASEP: *HD*



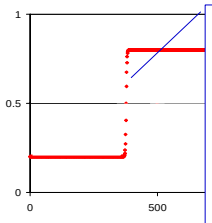
***HD*:** α=3/4, β=1/4, L=1000, N_x/L=0.75

Constrained TASEP: *SP*



***SP*:** α=1/4, β=1/4, L=1000, N_x/L=0.5

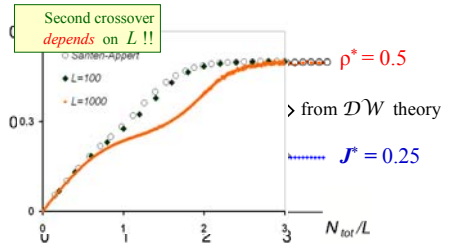
Domain Wall Theory



"domain wall"
- located at k, but wanders
- driven left/right by currents via α/β

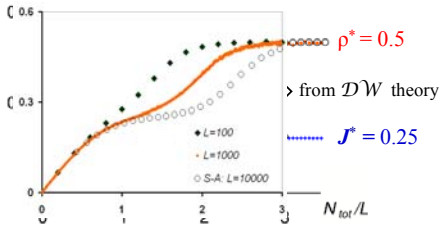
for domain wall theory
- write drift in terms of α,β
- write master eqn for $P(k,t)$
- steady state solution is simple *exp*
- get $\langle N \rangle$ in terms of ***α tanh(…)*** and β
- replace N in (…) by $\langle N \rangle$, then
- solve self consistent eqn for $\langle N \rangle$

Constrained TASEP: *SP*



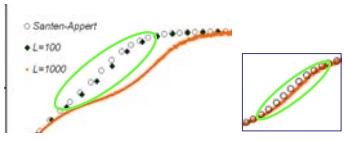
***SP*:** α=1/4, β=1/4, L=1000, N_x/L=0.5

Constrained TASEP: *SP*



***SP*:** α=1/4, β=1/4, L=1000, N_x/L=0.5

Constrained TASEP: *SP*



- Such small disagreements seem trivial…
- …BUT this picture is ***deceptively*** good! and another story emerges.

Constrained TASEP: *SP*

- Fluctuations are clearly important for ***SP***
- …but they must be ***suppressed*** by the overall constraint.
- Suppression comes about through the feedback mechanism, i.e., $\alpha(N_{tot}-N)$
- Can see this even in the *LD* regime: Gaussians of $P(N)$ have narrower widths.
- Closer to *SP*, it leads to ***shock localization***.

Constrained TASEP: *HD SP*

- Generalize DW to account for feedback…
- …quick reminder of DW theory:

$$\partial_t P(k,t) = D_+ P(k-1,t) + D_- P(k+1,t) - (D_+ + D_-)P(k,t)$$

plus ***reflecting*** boundary conditions

position of DW: $\in [1,L]$

$$D_+ = \frac{j_+}{\rho_+ - \rho_-} = \frac{\beta(1-\beta)}{1-\beta-\alpha}$$
$$D_- = \frac{j_-}{\rho_+ - \rho_-} = \frac{\alpha(1-\alpha)}{1-\beta-\alpha}.$$

Constrained TASEP: *HD SP*

- Generalize DW to account for feedback by
- a simple approximation:
- Promote

$$\alpha(N_{tot}-\langle N\rangle) \Rightarrow \alpha(N_{tot}-N)$$

- Relate N to k, the DW position
- Have k dependent drift coefficients

Constrained TASEP: *HD SP*

$$\partial_t P(k) = D_{+,k-1}P(k-1) + D_{-,k+1}P(k+1) - (D_{+,k}+D_{-,k})P(k)$$

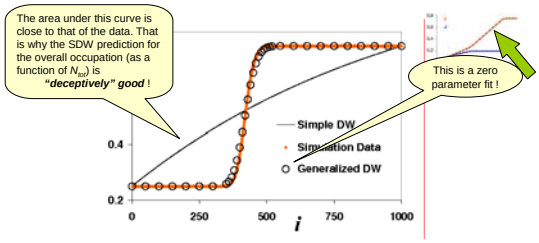
$$P^*(k) = \left(\sum_{m=k_{\min}}^{k-1} \prod_{\ell=m+1}^{k} \frac{D_{-,\ell}}{D_{+,\ell-1}} + 1 + \sum_{m=k+1}^{L} \prod_{\ell=k+1}^{m} \frac{D_{+,\ell-1}}{D_{-,\ell}} \right)^{-1}$$

From here, we can find the density profile ρ_i…

$$\rho_i = \sum_{k=k_{\min}}^{i} (1-\beta)P^*(k) + \sum_{k=i+1}^{L} \alpha_{\text{eff},k} P^*(k)$$

… and the result is

Constrained TASEP: *HD*

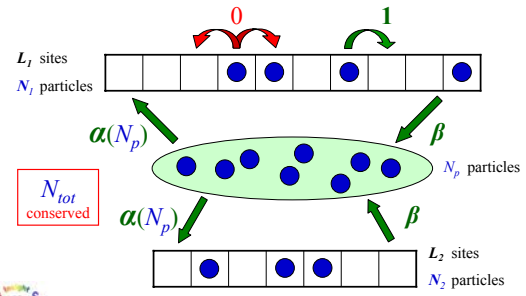


This GDW theory captures the essence of ***shock localization.***

Constrained ***single*** TASEP

- Generalized DW theory is excellent at predicting properties of the stationary state.
- Dynamics remains more challenging, e.g., new puzzles associated with the Power Spectrum of $N(t)$.

Constrained two TASEPs

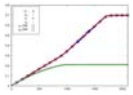


Constrained two TASEPs

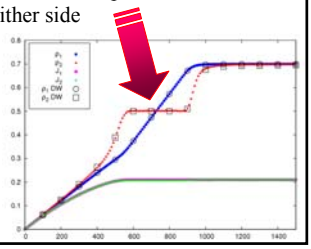
- For $\alpha(N_p)$, keep *tanh* function with $N_\times = \rho^*(L_1+L_2)/2$
- $L_1 = L_2$ not much different from single case...
  - ***except*** for motion (anticorrelated) of DWs
  - de-localization; flat profiles recovered
  - "intrinsic" profile (from shifted averages) unchanged
- $L_1 \neq L_2$ shows new feature...
  - for ***HD***, there are ***five regimes*** as N_{tot} increases
  - smaller chain has a central plateau + 2 crossovers

Constrained two TASEPs

- $L_1 = 10L_2 = 1000$ ***HD*** with α=0.7, β=0.3
  - ***five regimes*** as N_{tot} increases
  - smaller chain has a "central plateau" and crossovers on either side



$L_1 = L_2 = 1000$



Constrained two TASEPs

- *Rough* intuitive picture for new feature
- *Excellent* DW theory for two TASEPs
  - write master equation for $P(k_1, k_2; t)$
  - α_{eff} depends only on N_1+N_2 and so, $K \equiv k_1+k_2$
  - rates in ME satisfy detailed balance
  - stationary $P^*(k_1,k_2)$ "equilibrium-like" and so...
  - exactly solvable (with no fit parameters!)
  - ***predicts*** profiles, overall densities, etc.
  - generalized to ***any number*** of TASEPs

Constrained many TASEPs

- DW theory ***agrees well*** with MC 3 TASEPs
- No qualitatively new features … at least so far!
- Interesting analogy with canonical ensemble
  - constant K ($\equiv k_1+k_2+\ldots+k_M$) sheets have equal P^*
  - constant E sheets have equal P^*: $E \Leftrightarrow K$?
  - T controls E $\Leftrightarrow$ N_{tot} controls K ?
- If α of various TASEPs differ, then P^* is a genuinely *nonequilibrium* distribution.

⋮

Recap of 3rd Extension

- "Finite resources" provides many new interesting issues for TASEP
- Some aspects understood; but puzzles remain
- Many further extensions, e.g., extended particles, non-uniform hopping rates, competition for other resources (e.g., aa-tRNA), …
- Even wider afield, e.g., multi-species, multi-lanes
- A long way to go, just to describe one cell
- …let alone many cells that make up one living being!