A Model for Cell Proliferation in a Developing Organism

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ACEMS Research Group Meeting

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Disclaimer. Work in progress!

Starting point. Talks given by Kerry Landman at recent UQ Mathematics Colloquia (August 2015 and July 2016).

The model in question is described in . . .

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Modelling. We investigate a one-dimensional lattice model for tissue growth with lattice spacing Δ. (A continuum model is obtained in the limit as $\Delta \to 0$.)

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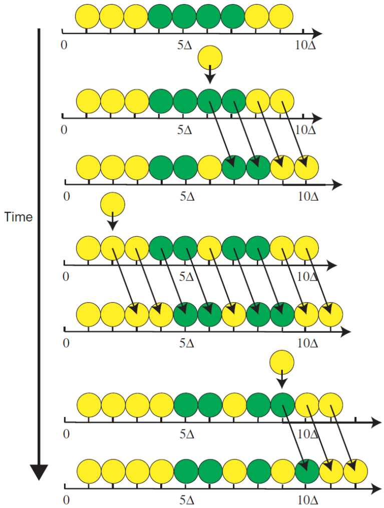

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The state $\boldsymbol{X}(t)$ of the system at time t is a binary vector of length $N(t)$, whose i-th entry is 1 or 0 according to whether site i is occupied by a marked cell. It takes values in the (countable) subset of $\{0,1\}^{\mathbb{N}}$ whose elements have only finitely many 1s.

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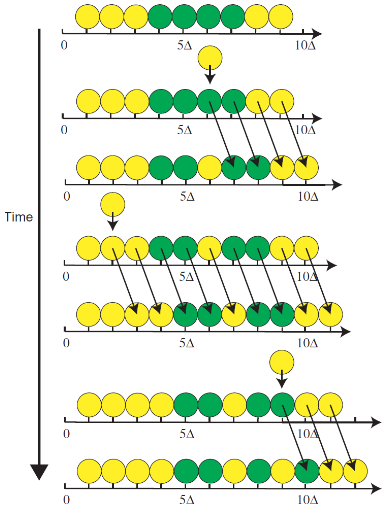

Q & A. What can we say about the model?

- The process $(\boldsymbol{X}(t),\, t \geq 0)$ is a
- Consider a particular marked cell. Is its position $I(t)$ at time t Markovian?
- If that cell is in position i, it moves to the right at rate
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- Therefore, the distance travelled by any particular marked cell up to time t (its position relative to its starting site j) has a distribution.
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- Finally note that if we start with all marked cells in adjacent sites, then, at any future time, the gaps between them will be *independent*, and thus the positions of the marked cells at any fixed time t will follow a *discrete renewal process* with negative binomial lifetimes. (We have not exploited this fact in our analysis so far, but we have plans!)

The approach of Hywood, Hackett-Jones, and Landman

They focussed attention on the *expected occupancy* (*occupancy probability*) $C_i(t)$, the chance that site i is occupied by a marked cell at time t, and derived a continuum model for *occupation density* $C(x, t)$ at position x (taking Δ to its limit 0).

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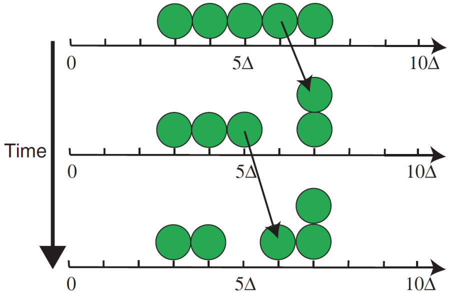

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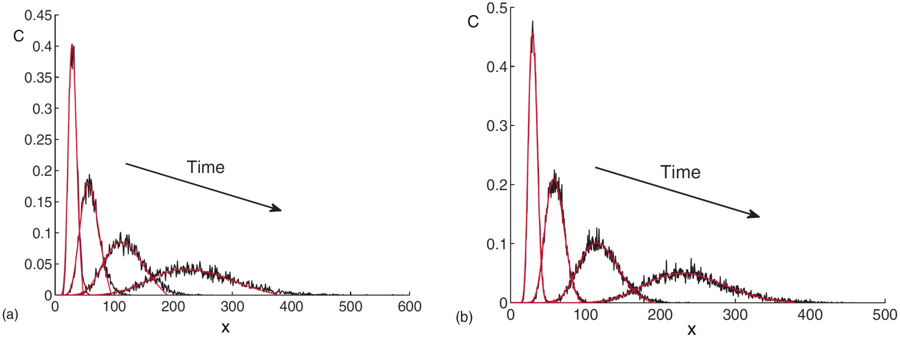

Solutions, in red, to $\dfrac{\partial}{\partial t}C(x,t) = -\lambda\dfrac{\partial}{\partial x}[xC(x,t)] + \dfrac{\lambda\Delta}{2}\dfrac{\partial^2}{\partial x^2}[xC(x,t)]$,

and expected occupancy estimates (1000 runs), in black, for $t = 1, 2, 3, 4$, with $L(0) = 24$, $\lambda = 0.69$, and marked cells initially in $[12, 18]$: (a) $\Delta = 1$, (b) $\Delta = 1/2$.

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If the marked cells are initially located at adjacent sites $j = r+1, \ldots s$, the expected occupancy for site k at time t is

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To see this, generate a Yule process starting j using an ensemble of independent rate-λ Poisson processes $\{N_i^{(j)}(t),\ i = 1, 2, \dots\}$ (one for each site i), and superimpose these processes ($s - r$ of them).

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If the $\{N^{(j)}\}$, $j = r+1, \ldots s$, are *independent* ensembles of Poisson processes, we get trajectories the approximating model. However, if they are *the same* ensemble, we get trajectories of the original model. The above formula is a simple consequence of noticing that the approximating model is the *empirical process*, which counts the numbers of "particles" in each state.

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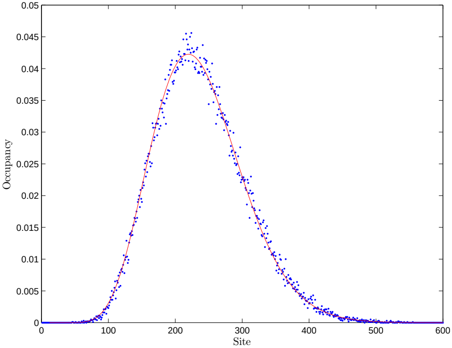

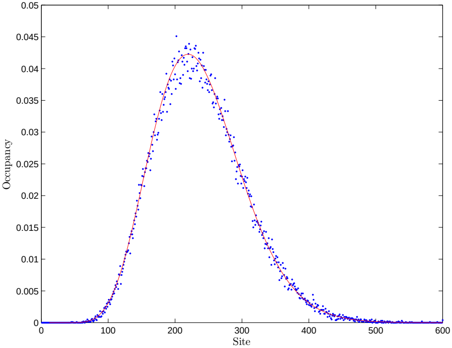

Estimates (blue), based on $10,000$ runs, of the expected occupancy of the proliferation process (left) and the corresponding ensemble of Yule processes (right) over 600 sites, with $\Delta = 1$, $t = 4.0$, proliferation rate $\lambda = 0.69$, and initially 7 marked cells located at sites 12 up to 18. Also plotted (solid red) is $C_i(t)$ for $i = 1, \ldots, 600$.

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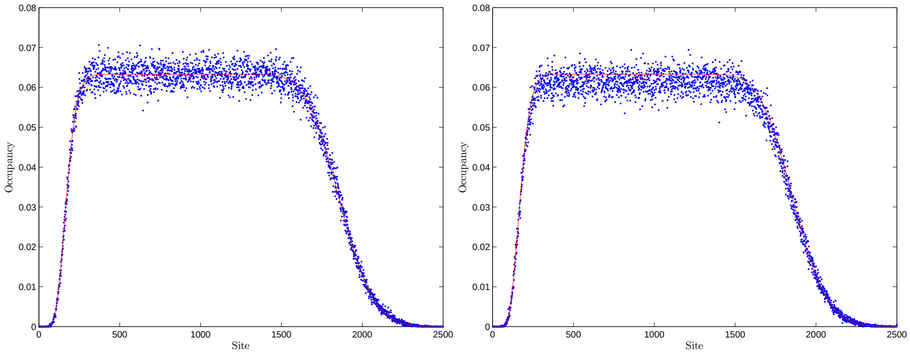

Estimates (blue), based on $10,000$ runs, of the expected occupancy of the proliferation process (left) and the corresponding ensemble of Yule processes (right) over $2,500$ sites, with $\Delta = 1$, $t = 4.0$, proliferation rate $\lambda = 0.69$, and initially 107 marked cells located at sites 12 up to 118. Also plotted (solid red) is $C_i(t)$ for $i = 1, \ldots, 2,500$.

The occupancy density

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Suppose cells are situated at points in the interval $[a,b]$ with equal spacing Δ (>0):

$$a+\Delta, a+2\Delta, \ldots, a+N\Delta \ (=b),$$

where $N=(b-a)/\Delta$ is the number of points. The idea is that the initial "cell mass" $b-a$ is distributed evenly among these N points. We are now interested in the expected occupancy at position x at time t, namely

$$C_\Delta(x,t) = \sum_{j=a/\Delta+1}^{\min\{b/\Delta, x/\Delta\}} \binom{x/\Delta - 1}{x/\Delta - j} e_t^j (1-e_t)^{x/\Delta - j}.$$

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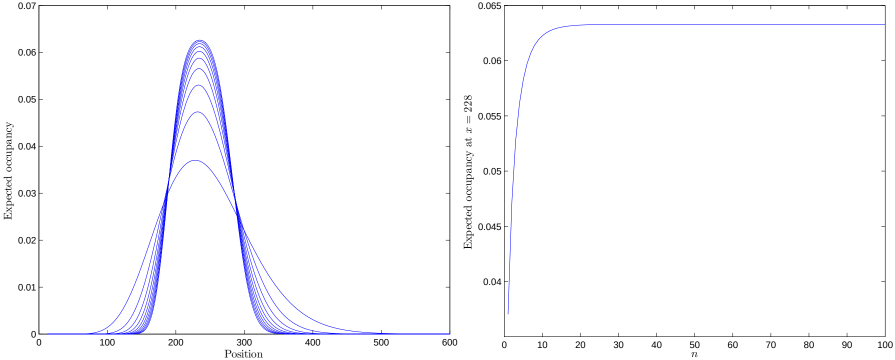
What happens to $C_\Delta(x,t)$ as $\Delta \to 0$?

The occupancy density



The left-hand pane shows $C_\Delta(x,t)$ at $t = 4.0$ for values of Δ from 1 down to $1/n$, where $n = 10$. The initial cell mass is on the interval $[12, 18]$, and $\lambda = 0.69$. The right-hand pane shows $C_\Delta(x,t)$ for $x = 228$ (approximately where the peaks occur) for values of $\Delta = 1/n$ up to $n = 100$. The code uses `nbinpdf(k-j,j,e)`.

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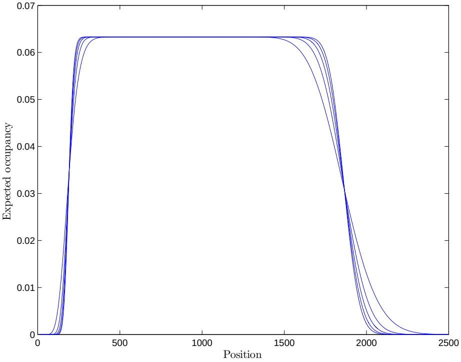

$C_\Delta(x,t)$ at $t = 4.0$ for values of Δ from 1 down to $1/n$, where $n = 5$. The initial cell mass is on the interval $[12, 118]$, and $\lambda = 0.69$. Decreasing Δ corresponds to an increasing amount of flatness in the curves and decreasing tail mass.

Recall that

$$C_\Delta(x,t) = \sum_{j=a/\Delta+1}^{\min\{b/\Delta, x/\Delta\}} \binom{x/\Delta - 1}{x/\Delta - j} e_t^j (1-e_t)^{x/\Delta - j}, \qquad \text{where } e_t = \exp(-\lambda t).$$

Suppose that all quantities are chosen so that $i := x/\Delta - 1$, $l := a/\Delta - 1$, $m := b/\Delta - 1$, and $n := (b-a)/\Delta = m - l$ are integers, and in particular when Δ becomes small.

The occupancy density - an approximation

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Then, we may write

$$C_\Delta(x,t) = \sum_{j=1}^{\min\{n, i-l\}} \binom{i}{i-l-j} \theta^{j+l+1}(1-\theta)^{i-l-j}, \qquad \text{where } \theta = e_t,$$

noting that i, l, m, and n, increase at the same rate when $\Delta \to 0$, and in particular, $l/i \to a/x$ and $m/i \to b/x$.

Next observe that

$$C_\Delta(x,t) = \theta \sum_{j=l+1}^{\min\{n+l,i\}} \binom{i}{j} \theta^j (1-\theta)^{i-j} = \theta \Pr(l+1 \le S_i \le \min\{n+l,i\}),$$

where S_i has a binomial $B(i,\theta)$ distribution ($\theta = \exp(-\lambda t)$).

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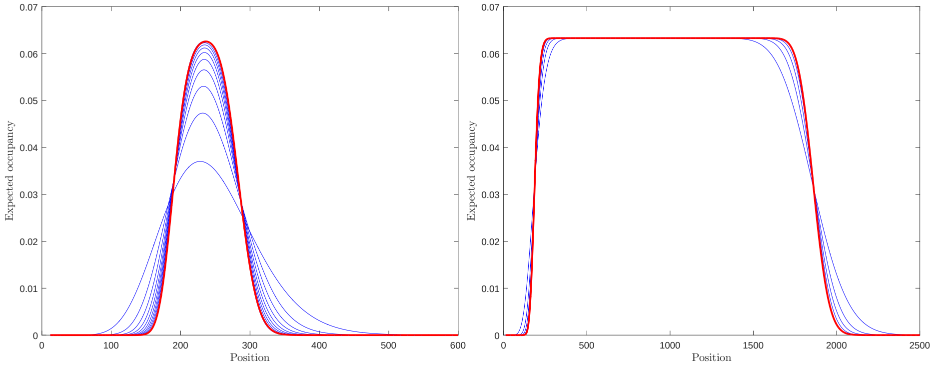
where S_i has a binomial $B(i,\theta)$ distribution ($\theta = \exp(-\lambda t)$).

So, we may employ the normal approximation to the binomial distribution to approximate $C_\Delta(x,t)$ where Δ is small (and hence i is large). We get $C_\Delta(x,t) \simeq C_{\text{approx}}(x,t)$, where

$$C_{\text{approx}}(x,t) = \theta \Pr\left(\frac{a/x - \theta}{\sqrt{\theta(1-\theta)}}\sqrt{i} \le Z \le \frac{\min\{b/x, 1\} - \theta}{\sqrt{\theta(1-\theta)}}\sqrt{i} \right),$$

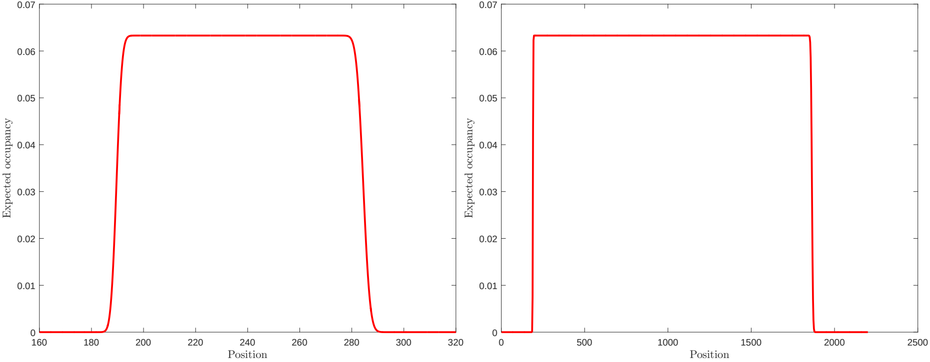
where Z is a standard normal random variable.

The occupancy density - normal approximation



Evaluation of $C_\Delta(x,t)$ at $t = 4.0$ with $\lambda = 0.69$, and with initial cell mass on the interval $[12, 18]$ (left pane) and on the interval $[12, 118]$ (right pane). The corresponding normal approximation is shown in bold red. The code uses `normcdf`.

The occupancy density - normal approximation



The normal approximation with Δ quite small ($\Delta = 0.001$). A clearer picture is emerging of the shape of occupation density curve $C(x, t)$.

The occupancy density

Theorem. If, initially, the marked cells lie in the interval $[a, b]$, the occupation density at time t is given by

$$C(x,t) := \lim_{\Delta \to 0} C_\Delta(x,t) = \begin{cases} 0 & \text{if } 0 < x < ae^{\lambda t} \\ \frac{1}{2}e^{-\lambda t} & \text{if } x = ae^{\lambda t} \\ e^{-\lambda t} & \text{if } ae^{\lambda t} < x < be^{\lambda t} \\ \frac{1}{2}e^{-\lambda t} & \text{if } x = be^{\lambda t} \\ 0 & \text{if } x > be^{\lambda t}. \end{cases}$$

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Proof. Recall that $C_\Delta(x,t) = \theta \Pr(l + 1 \le S_i \le \min\{m, i\})$, where S_i has a binomial $B(i, \theta)$ distribution ($\theta = \exp(-\lambda t)$), and $l/i \to a/x$ and $m/i \to b/x$ as $i \to \infty$.

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We use Theorem 2 of . . .

> Arratia, R. and Gordon, L. (1989) Tutorial on large deviations for the binomial distribution. *Bulletin of Mathematical Biology* 51, 125–131.

. . . which provides an approximation for $\Pr(S_i \ge ai)$, $a > 0$, when i is large.

The result of Arratia and Gordon

Let $H(\epsilon, \theta)$ be *Kullback-Leibler divergence* between an ϵ-coin and a θ-coin:

$$H(\epsilon, \theta) = \epsilon \log \left(\frac{\epsilon}{\theta} \right) + (1 - \epsilon) \log \left(\frac{1 - \epsilon}{1 - \theta} \right).$$

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Suppose S_i has a binomial $B(i, \theta)$ distribution. If $\theta < \epsilon < 1$,

$$\Pr(S_i \geq i\epsilon) \sim \frac{1}{(1-r)\sqrt{2\pi\epsilon(1-\epsilon)i}}\, e^{-iH(\epsilon,\theta)}, \qquad \text{as } i \to \infty.$$

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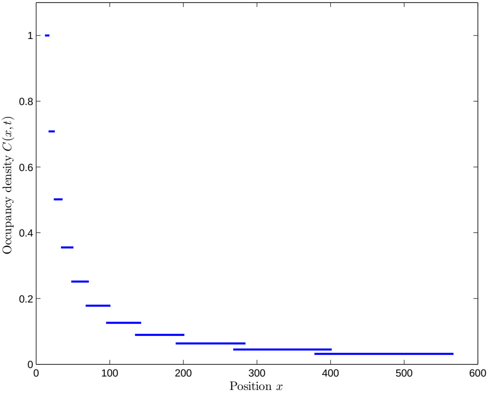
The occupancy density

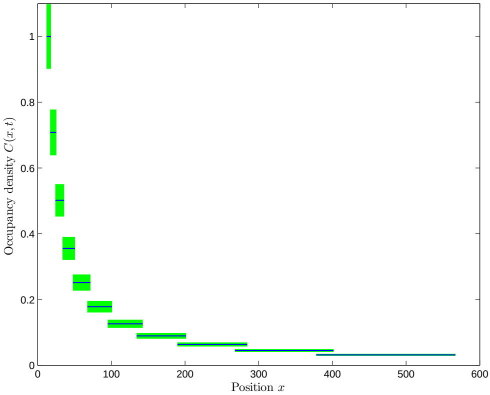
Theorem. If, initially, the marked cells lie in the interval $[a, b]$, the occupation density at time t is given by

$$C(x,t) := \lim_{\Delta \to 0} C_\Delta(x,t) = \begin{cases} 0 & \text{if } 0 < x < ae^{\lambda t} \\ \frac{1}{2} e^{-\lambda t} & \text{if } x = ae^{\lambda t} \\ e^{-\lambda t} & \text{if } ae^{\lambda t} < x < be^{\lambda t} \\ \frac{1}{2} e^{-\lambda t} & \text{if } x = be^{\lambda t} \\ 0 & \text{if } x > be^{\lambda t}. \end{cases}$$



Evaluation of the occupation density $C(x,t)$ at times $t = 0,\ 0.5,\ 1.0,\ \ldots,\ 5.0$, with $\lambda = 0.69$, and with initial cell mass on the interval $[12, 18]$.

The occupancy density



Evaluation of the occupation density $C(x, t)$ at times $t = 0, 0.5, 1.0, \ldots, 5.0$, with $\lambda = 0.69$, and with initial cell mass on the interval $[12, 18]$. The green bars indicate relative cell mass.

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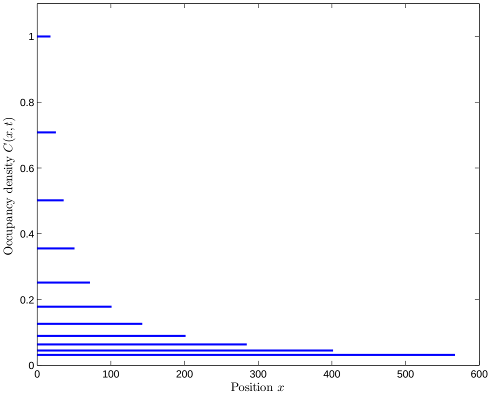

Evaluation of the occupation density $C(x,t)$ at times $t = 0, 0.5, 1.0, \ldots, 5.0$, with $\lambda = 0.69$, and with initial cell mass on the interval $[0, 18]$.

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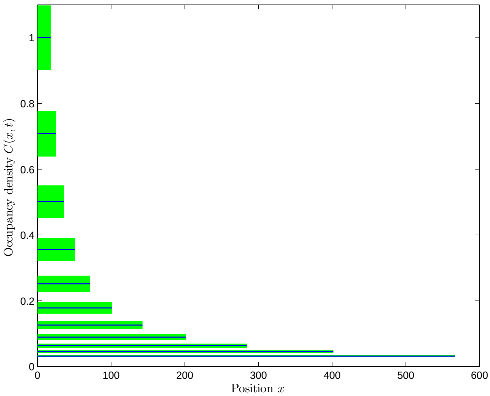

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